The Journal of
Thoracic and
Cardiovascular Surgery

VOLUME 38
SEPTEMBER 1959
NUMBER 3

Original Communications

STUDIES OF PULMONARY DIFFUSION AFTER OPEN HEART SURGERY

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SINCE the earliest days of open heart surgery with extracorporeal circulation, there have been reports of severe pulmonary complications developing after operation. While increasing experience has done much to reduce the incidence of these complications, a large proportion of patients still require assisted respiration, tracheostomy, and prolonged oxygen therapy during the postoperative period. It is correct perhaps to assume that any functional alteration in the lungs, resulting from extracorporeal circulation, is due to injury to the pulmonary capillaries or the alveolar membrane and that this is reflected in alterations of pulmonary gas diffusion. This report is concerned with measurements of the carbon monoxide diffusing capacity (D_{CO}) in human beings and in experimental animals before and after cardiopulmonary bypass. The "steady state" diffusing capacity[1] for carbon monoxide is ideally suited to the studies of these patients since it permits some assessment of ventilatory function, as well as the diffusing function of the lung, without requiring any unusual effort on the part of the patient.

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Supported in part by the Louisiana Heart Association and U.S. Public Health Service Grant HTS-5170, the Jones County Texas Tuberculosis Association, and the Tuberculosis Association of Greater New Orleans.

Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

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METHODS

Carbon monoxide diffusing capacity (D_{CO}) was determined by the method of Filley, MacIntosh, and Wright[1] with a few modifications. To minimize hypoxemia, the subjects inspired a gas mixture of 0.1 per cent CO in 30 per cent O_2 rather than the usual 0.1 per cent CO in air. Carbon dioxide pressure was calculated after determination of the pH, hematocrit, and CO_2 content of arterial blood. Seven adult patients had carbon monoxide diffusion studies done preoperatively and, on several occasions, after open heart surgery. Diagnoses in these patients are listed in Table I. Only 1 patient (No. 6) had any evidence of intrinsic pulmonary disease. This was marked by chronic cough with expectoration associated with excessive smoking. Determinations were additionally performed on 2 patients undergoing thoracotomy without cardiopulmonary bypass.

TABLE I. CLINICAL STUDIES

PATIENT NUMBER	INITIALS	AGE	DIAGNOSIS
1	H. D.	30	Aorta-RA fistula
2	Z. M.	47	Mitral insufficiency
3	J. M.	27	Aorta-RV fistula
4	N. C.	18	Atrial septal defect
5	H. S.	29	Ventricular septal defect
6	A. M.	52	Atrial septal defect
7	J. J.	32	Aortic stenosis
8	Y. F.	32	Mitral stenosis*
9	J. T.	65	Hiatus hernia*

*Not on extracorporeal circulation.

Preoperative and postoperative determinations of diffusing capacity were also performed on 5 mongrel dogs undergoing unilateral thoracotomy of 15 minutes' duration. In another group of 5 dogs, determinations (D_{CO}) were made before and after establishment of extracorporeal circulation without thoracotomy. This was done by inserting No. 18 Fr. polyethylene catheters into the right atrium through the common femoral and external jugular veins. These were connected to the venous line of a DeWall bubble oxygenator. Oxygenated blood was returned to the animal through a femoral artery. Two additional dogs were studied before and after cardiopulmonary bypass established through a right thoracotomy. In these animals, extracorporeal circulation and inflow occlusion were maintained for 15 minutes. In all animal experiments, a cuffed endotracheal tube was inserted. Animals were anesthetized with veterinary Nembutal 15 mg. per kilogram of body weight. Further anesthesia was provided by continuous intravenous administration of Nembutal in dilute solution (6 mg./c.c.) so that the respiratory rate was maintained at 18 to 30 per minute. Ventilation during thoracotomy in animals was maintained by an automatic respirator utilizing room air. The lungs were not inflated during cardiopulmonary bypass in dogs or patients.

A DeWall pump-oxygenator system was used in all animal experiments and in Patients 1 and 3. Oxygenation was obtained by bubbling 100 per cent

O_2 through the blood in this system. In the remaining patients, a Kay-Cross rotating disc oxygenator was used. In this system, oxygenation was secured by exposing blood to a mixture of 95 per cent O_2 and 5 per cent CO_2.

All patients subjected to open heart surgery in this study were considered good operative risks. Perfusions in all instances were conducted at maximum flow rates, that is, limited only by the volume of venous return. Satisfactory repair of all defects was accomplished with the exception of Case 2 in whom significant mitral regurgitation persisted after operation. No postoperative pulmonary complications of unusual magnitude appeared except in Case 2. Temporary atelectasis of the left lower lobe occurred in Case 6 and responded to bronchoscopic aspiration.

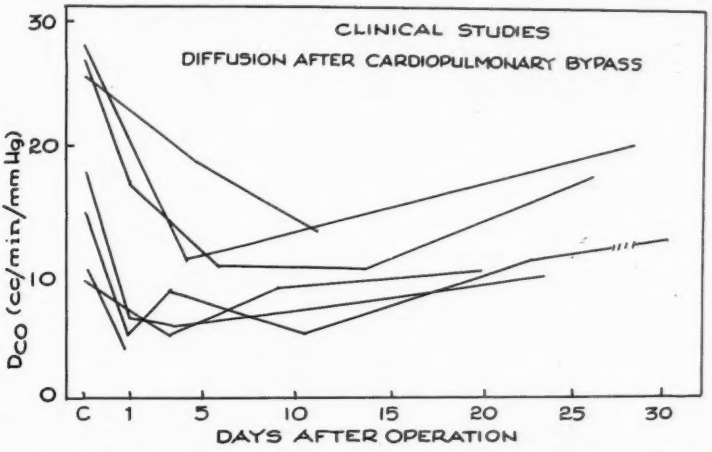

Fig. 1.—Carbon monoxide diffusing capacity before and after open heart operations. *C* on the ordinate represents a preoperative determination which may have been done 1 to 7 days before operation.

RESULTS

In each of the 7 patients, undergoing open heart surgery, there was an increase in total ventilation (V_L) after operation, but in no instance did it exceed 15 per cent of the predicted maximum breathing capacity (MBC) for the individual. Tidal volume (V_T) was essentially unchanged or reduced immediately following operation. The physiologic dead space (V_D) was increased in all patients except No. 5. In part, this could be accounted for on the basis of an increased frequency of respiration, but it more likely represented an unfavorable alteration of the ventilation-perfusion relationship in the immediate postoperative period. For the most part, alveolar ventilation (V_A) was effectively maintained. Two patients (Nos. 4 and 6) exhibited small reductions of V_A and there were increases of similar magnitude. Ventilation equivalent (V_{O_2} [c.c./min.] V_L [L./min.]) was within normal range, both before and after operation, in all cases except No. 2 in whom it was slightly

abnormal. Oxygen consumption increased somewhat after operation, usually from the fourth to the eleventh day, and then returned to control levels. The diffusion capacity for carbon monoxide, however, was uniformly reduced after operation to 25 to 40 per cent of preoperative values (Fig. 1). In 3 cases (Nos. 1, 3, and 4), the lowest values were still within the accepted range of normal for these laboratories. In the remaining 4 patients, depression to definitely abnormal levels was observed. In 4 patients (Nos. 1, 3, 4, and 5), the control values were at the upper limits of normal. All of these patients had left-to-right shunts of considerable magnitude. In only 1 patient (No. 6) with a left-to-right shunt was the D_{CO} reduced below normal prior to operation, and this patient had chronic lung disease.

TABLE II. CLINICAL STUDIES

PATIENT	DAYS	V_L	V_T	V_D	V_A	V_{O_2}	pCO_2	D_{CO}
No. 1	0	4.39	334	69	2.54	156	40	25.7
	4	6.36	338	122	3.24	196	38	19.3
	11	5.80	386	159	3.29	159	34	13.9
No. 2	0	4.22	336	95	2.46	138	44	10.4
	1	6.82	272	103	3.11	142	35	3.8
No. 3	0	2.64	459	90	1.82	115	40	27.6
	1	4.00	317	118	1.46	137	47	17.4
	5	5.49	464	165	3.01	163	40	10.7
	13	5.08	505	132	3.29	164	41	10.5
	26	3.93	546	121	2.73	144	41	17.9
No. 4	0	3.97	506	127	2.90	124	36	28.0
	4	4.01	295	98	2.08	170	46	11.4
	13	4.65	387	152	2.31	147	45	14.5
	27	3.64	364	134	2.10	123	43	19.6
No. 5	0	3.20	280	68	1.90	132	42	18.9
	1	3.37	278	70	1.90	117	41	7.0
	3	3.37	303	78	2.00	129	40	5.9
	24	4.14	333	83	2.50	157	37	10.0
No. 6	0	4.08	377	73	2.78	136	35	10.0
	3	4.91	308	134	2.05	153	43	5.2
	9	4.76	380	132	2.53	146	41	9.2
	21	3.90	457	154	2.01	131	40	10.6
No. 7	0	5.62	546	181	3.26	188	39	15.5
	1	8.73	424	226	3.14	215	39	5.4
	3	7.94	466	223	3.38	236	45	8.5
	10	6.26	520	212	3.17	229	42	5.8
	24	4.96	520	210	2.80	166	40	12.0
	37	5.20	552	212	2.78	140	37	13.8
No. 8	0	4.93	368	99	3.6	174	42.5	12.7
	1	3.77	264	66	3.42	140	43	5.31
	4	4.37	306	68	3.38	176	44	7.22
	11	4.79	278	58	3.8	154	39.5	7.26
	17	4.04	285	66	3.1	152	42	11.7
No. 9	0	3.32	598	176	2.32	149	40	16.3
	1	1.80	275	82	1.27	113	43	7.64
	5	2.87	474	140	2.02	147	39	15.8
	8	3.40	465	141	2.32	153	35	14.6

V_L = Minute ventilation (L./min./M.²)
V_T = Tidal volume (c.c.)
V_D = Dead space (c.c.)
V_A = Alveolar ventilation (L./min./M.²)
V_{O_2} = Oxygen consumption (c.c./min./M.²)
D_{CO} = Diffusing capacity for CO (c.c./min./mm. Hg)

In 4 patients of this series, D_{CO} was measured using 0.1 per cent carbon monoxide in room air. In these 4 patients, the lowest values of D_{CO} were associated with the development of arterial hypoxemia. This hypoxemia was moderate in degree, ranging from 74 to 88 per cent.[2] Values for pH were normal or slightly elevated in those patients who had pronounced increases in alveolar ventilation. The pCO_2 was closely related to the alveolar ventilation which it followed in the expected manner. One patient studied before

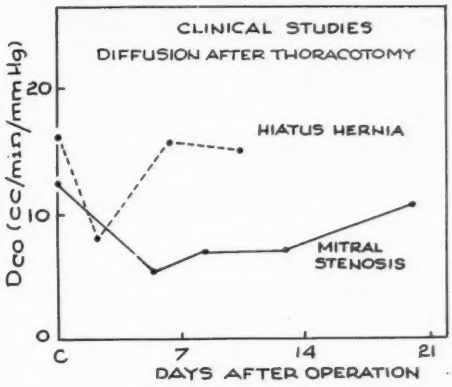

Fig. 2.—Carbon monoxide diffusing capacity before and after thoracotomy without cardiopulmonary bypass.

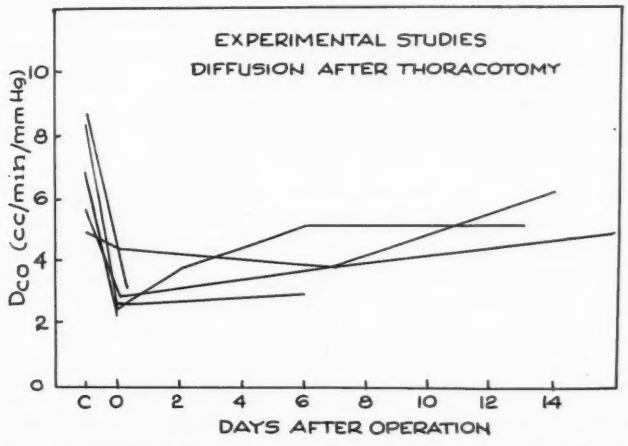

Fig. 3.—Carbon monoxide diffusing capacity before and after unilateral thoracotomy in the dog.

and after a closed valvulotomy for mitral stenosis showed a pattern of respiratory function after operation similar to that of the patients undergoing open heart surgery, in that the extent and duration of depression of D_{CO} was about the same. Another patient studied before and after transthoracic repair of hiatus hernia developed a marked depression of the D_{CO} on the first postoperative day, which reverted to normal, however, by the fifth postoperative

day (Fig. 2). This patient, unlike the open heart cases, had moderate alveolar hypoventilation after operation.

In 4 of 5 dogs subjected to unilateral thoracotomy, there was a depression of the D_{CO} on the first postoperative day with a gradual return to control

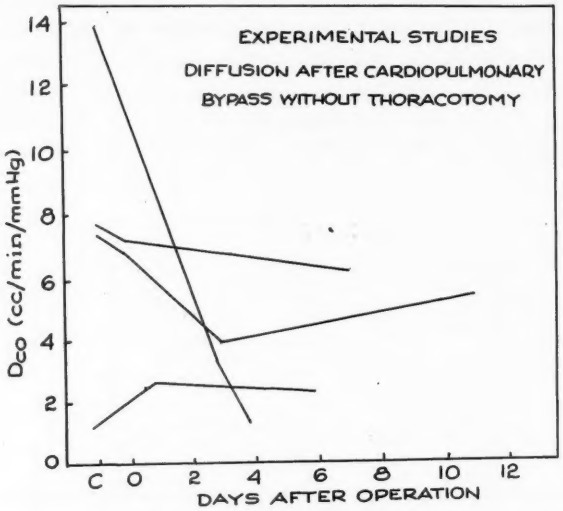

Fig. 4.—Carbon monoxide diffusing capacity before and after perfusion without thoracotomy in the dog.

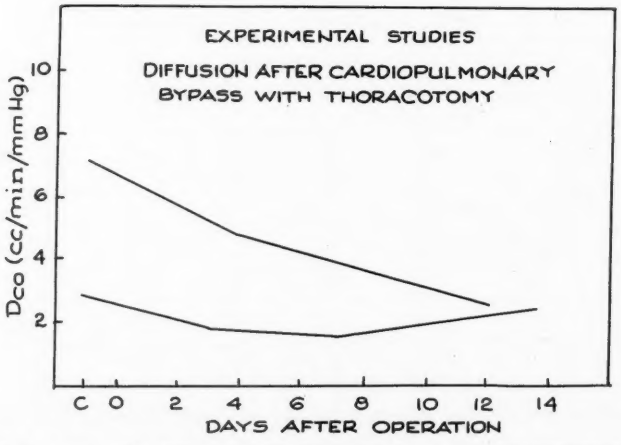

Fig. 5.—Carbon monoxide diffusing capacity before and after cardiopulmonary bypass with right thoracotomy in the dog.

levels (Fig. 3). The fifth dog showed essentially no change. In 2 of the 4 animals tested before and after perfusion without thoracotomy, there was essentially no change in the D_{CO} (Fig. 4). In 1 dog, a marked depression of

the D_{CO} had developed by the third postoperative day when he was again tested. It would appear that there is no consistent alteration produced by this procedure. Unilateral thoracotomy with cardiopulmonary bypass performed on 2 additional dogs resulted in decreased D_{CO} which was still present in 1 animal 12 days after operation (Fig. 5). In the other animal, the D_{CO} had returned to normal levels by the fourteenth postoperative day. These animal studies indicate that a definite decrease in D_{CO} follows thoracotomy in the dog. The extent of this depression does not appear to be affected by the addition of cardiopulmonary bypass, although the duration of this decrease may be prolonged by perfusion.

DISCUSSION

It is a matter of considerable practical importance to determine the etiology of the depression of carbon monoxide diffusing capacity; to determine its significance in the postoperative course of patients after open heart surgery; and to determine the most effective means of either preventing or combating it.

The diffusing capacity is defined as the cubic centimeters of carbon monoxide passing from alveolar gas into the arterial blood each minute in relation to each millimeter of pressure difference between the alveolus and the blood. The factors which are known to influence the diffusing capacity of carbon monoxide are the thickness, physical properties, and the area of the surface across which the diffusion takes place. The effective area for diffusion further depends on the number and size of the functioning pulmonary capillaries.[3] The method used to determine D_{CO} does not differentiate these components.[4] In considering the possible reduction of the area of the membrane, certain factors come to mind. The D_{CO} could be reduced by a total reduction of lung volume although it is unlikely in this circumstance because of several observations. First, there is either no change or an increase in dead space after thoracic operation and cardiopulmonary bypass whereas one would expect a reduction in dead space with a total reduction of lung volume. There is, furthermore, no clinical evidence of reduction in lung volume. A reduction in diffusing capacity was observed under circumstances in which there was no evidence of atelectasis, diaphragmatic paralysis, effusion, pneumothorax, or anything else that would enroach on lung volume. A better explanation and one that is compatible with the observations here is that the reduction in D_{CO} is due to a reduced area of functioning pulmonary capillaries. In 5 of the 7 patients, a left-to-right shunt of varying size was present and in all of these patients, the pulmonary artery pressure was normal.[5] Resting values for D_{CO} were high and it may be assumed that pulmonary capillary blood flow was also high. Closure of the shunt, therefore, would tend to lower the D_{CO}. Reduction of D_{CO} on this basis should be instantaneous; that is, it should be maximal immediately after operation. In the cases observed, however, there was a continuing decrease in D_{CO} until the sixth to the tenth day, which would suggest that factors other than closure of the shunt were active. Among other factors which might reduce the available area would be a continuing decrease in the size of the

pulmonary capillary bed. Conclusive evidence regarding this could be determined by measuring the pulmonary artery pressure and the cardiac output postoperatively. If there is a progressive reduction in the size of the available pulmonary capillary bed this should be accompanied by increasing pressure in the pulmonary artery or a decrease in cardiac output or a combination of these two factors.

It is probable that the observed reduction in D_{CO} is due, at least in part, to an alteration in the characteristics of the alveolo-capillary membrane itself. Several factors must be considered of etiological significance. Among these are the prolonged inhalation of high concentrations of oxygen, the use of positive pressure during anesthesia, mechanical trauma to the lungs from handling, drying, etc., and factors introduced in the technique of perfusion. It is recognized that injury to the pulmonary membrane does occur, as detailed in the reports of Kolff[6] and Muller[7] and their associates. The histologic lesions described by Dodrill[8] probably also fall in this category of injury secondary to the technique of perfusion or possibly to agents employed in perfusion. This would not, however, account for the decreased diffusing capacity observed after thoracotomy alone and it is probable that other factors related to operations within the thorax are at least as important in this regard as overloading of the pulmonary circulation during perfusion. All of these factors relating to alterations in the pulmonary membrane and in pulmonary blood flow are susceptible to evaluation; however, such studies would be difficult to carry out in human beings since exercise and sampling of mixed venous blood would be necessary.

The difference observed between these patients and patients spontaneously developing an alveolar capillary block are of more immediate interest and importance. It is characteristic of patients with alveolar capillary block that hyperventilation, particularly alveolar hyperventilation, is present. This is presumably due to hypoxemia and is mediated through stimulation of the chemoreceptor system. Because of the greatly increased diffusibility of carbon dioxide, these patients invariably have a reduced pCO_2. In the patients of this series in whom measurements were performed, using 0.1 per cent carbon monoxide in room air, definite hypoxemia was present, corresponding to the depression in D_{CO}. The response of these patients to hypoxemia was ineffectual. It should be emphasized that alveolar ventilation was normal or at least very near the preoperative measurement for the individual, yet there were a need and a stimulus for the development of hyperventilation, but this did not take place. The cause for this failure of response is not clear. It may be due to reflex inhibition of respiration by stimuli arising from the incision and from the areas of pleuritis. There may be additional inhibition of the chemoreceptor system by narcotics. Another possibility that must be considered is that some form of reversible damage to the chemoreceptor system has occurred as a direct result of operation or of perfusion.

Since interference with diffusion after operation may be severe and since it has been demonstrated to be entirely reversible, proper management of these

patients during the period of maximum depression is important. This particular group of patients was selected for study because of the fact that they had tolerated their operative procedure well and were convalescing satisfactorily, the lone exception being patient No. 2. It is probable that these changes occur to an even more marked degree in those patients in whom respiratory inadequacy is evident postoperatively. It would appear that treatment should involve elevation of the partial pressure of oxygen in the alveoli and that this could be accomplished by decreasing the dead space, by the administration of high concentrations of oxygen, and by increasing the tidal volume. Decrease in the dead space can be effected by means of tracheostomy and the delivery of an increased tidal volume can be accomplished by use of respirators, particularly those designed to deliver a specific tidal volume. These measures, while the best available for treatment of postoperative hypoxemia, must be employed with reservation until their effects on cardiac output, pulmonary blood flow, and the alveolar capillary membrane in postoperative patients are known.

SUMMARY

The diffusing capacity of carbon monoxide has been studied in 7 patients before and after open intracardiac operations, in 1 patient after closed mitral valvulotomy, and in 1 patient after transthoracic repair of a hiatus hernia. Depression of D_{CO} followed all of these operations in the immediate postoperative period. After the intracardiac procedures, this depression persisted for 6 to 14 days. There was a rapid return to a normal D_{CO} in the patient undergoing hiatal herniorrhaphy.

The effect of thoracotomy alone, cardiopulmonary bypass alone, and thoracotomy with cardiopulmonary bypass was studied in a group of dogs. All animals demonstrated an immediate postoperative reduction to D_{CO} and this appeared to be of longer duration in the animals additionally subjected to cardiopulmonary bypass. Cardiopulmonary bypass alone was followed by no consistent changes in the D_{CO}.

The desirability of determining the relative contribution of membrane damage and altered pulmonary circulation to the diffusion defect is evident. The inadequacy of patient response to this defect is striking. Therapy consists in reducing dead space, administration of high concentrations of oxygen, and increasing the tidal volume.

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Discussion

DR. JOHN H. GIBBON, JR., Philadelphia, Pa.—I can't let this nice paper go without making some remarks. As usual, it is an excellent study from Dr. Creech's group.

It is a field which has interested me for quite a number of years. I believe that postoperative pulmonary dysfunction after cardiopulmonary bypass accounts for a good deal of morbidity and mortality.

It appears to me, as Rubin Lewis sitting beside me said, that the depression of pulmonary diffusion lasts about as long as the respiratory excursions are limited by the pain of the operative wound. There is no paralysis of the diaphragm. There is no accumulation of blood or air in the pleural cavity, but there is limitation of respiratory activity from pain, lasting about 8 to 10 days. I wonder whether this depression of CO_2 diffusion doesn't parallel the period of wound healing. A nice check would be to do a lower abdominal laparotomy and see whether the same interference with CO_2 diffusion occurs.

I would like to again congratulate the authors on a very excellent paper.

DR. JOHN C. JONES, Los Angeles, Calif.—I would just like to ask the authors if they employed the use of helium with oxygen in the treatment of any of these patients. Would it not be worth while trying?

DR. GEORGE W. WRIGHT, Cleveland, Ohio.—Those of you who have never had to work with this technique probably don't appreciate the difficulties and the obstacles that one has to overcome in such a study.

I am interested in asking the authors what the range of variation is for this technique in their hands in normal individuals, and certainly in the preoperative group. When we were developing this method we found that we were unable to repeat duplicate runs with better than about a 10 to 15 per cent variation. I think this will have some bearing on the magnitude of the changes shown in this study, but I don't want to infer that this would bear on the direction of change.

DR. EDWARD J. BEATTIE, JR., Chicago, Ill.—I enjoyed this very excellent presentation.

There is one comment that I would like to add. Dr. Archer Gordon, when working in our laboratory, studied patients having major abdominal surgery, over a period of several days postoperatively. He found that although the patient was doing well clinically, most of the patients in the course of 48 hours postoperatively had arterial oxygen saturations of 90 per cent or below. I do not believe that this problem is confined to chest surgery.

DR. SCHRAMEL (Closing).—I should like to thank Drs. Gibbon, Jones, Wright, and Beattie for their comments.

To answer Dr. Gibbon, it is certainly true that this does parallel the healing of the wound and this could represent a total reduction of lung volume. However, alveolar ventilation was normal in these patients, and we have no definite evidence as to the over-all size of

the alveolar capillary membrane after operation, other than this study. It is possible that reducing the area on the basis of splinting could occur.

Dr. Jones, we did not use helium in any of these patients postoperatively.

Dr. Wright, our range of normal in these patients—we used essentially the same levels as observed by you. Our variation on preoperative determinations in the same individuals runs about 10 to 15 per cent. The direction of variation, as you pointed out, however, was all in the same way, all downward, and I think if you just moved the whole thing up or down 15 per cent it wouldn't make a great deal of difference.

We have not conducted these measurements in patients after abdominal surgery.

CLINICAL RESULTS OF CORRECTION UNDER HYPOTHERMIA OF ATRIAL SEPTAL DEFECTS AND PULMONARY VALVULAR STENOSIS

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THE METHODS for surgical correction of intracardiac lesions have undergone a rapid transition from the initial blind or closed methods to the present-day open heart procedures utilizing cardiopulmonary bypass with extracorporeal circulation. The initial open heart procedures were made possible by general hypothermia which results in reduced body metabolism and allows circulatory occlusion for limited periods of time without brain damage.[1, 2] The use of hypothermic techniques has not enjoyed widespread acceptance, primarily because of the short time allowed for intracardiac manipulation and the danger of refractive ventricular fibrillation. In spite of these potential difficulties, a number of surgical centers have been enthusiastic advocates, and they have reported highly acceptable series of operations using this technique.[3, 4, 5] The technique is now used primarily for the correction of pulmonary valvular stenosis, atrial septal defects of the secundum type, and for the less complicated varieties of abnormal pulmonary venous drainage usually associated with high atrial septal defects. The present trend, however, in many centers is to employ cardiac bypass techniques for all intracardiac procedures. The purpose of this paper is to review the clinical effectiveness of the hypothermic technique which we have used and, in particular, to assess the surgical problems involved and the long-term clinical results.

CLINICAL MATERIAL

During the past 3½ years, 35 patients have had, under hypothermia, repair of atrial septal defects, pulmonary valvular stenosis, and partial anomalies of the pulmonary venous return. These patients will be considered in two groups: first, valvular pulmonic stenosis, and second, atrial septal defects.

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Supported in part by grants from the U.S. Public Health Service (Grant H-2572[C3]) and the Tuberculosis and Health Association of Rochester, New York.

Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

Valvular Pulmonic Stenosis.—Nineteen patients have had pulmonary valvulotomies. Three of these had significant ostium secundum defects with left-to-right shunting, and 1 had a partial anomaly of the venous return, with the right pulmonary veins draining into the right atrium. Fourteen patients were in the pediatric age range from 5 to 14 years, and 5 were adults from 19 to 37 years. All patients had definite symptoms; the most common were decreased exercise tolerance with fatigability and dyspnea with exertion. Intermittent palpitation, chest pain, and cyanosis were present in several. One girl of 19 years had termination of a pregnancy because of shortness of breath, before being referred for evaluation. One man of 30 years of age had frank congestive heart failure.

The patients were all well developed except 1. All patients had a palpable systolic thrill high along the left sternal border and a long harsh systolic murmur. All patients had a markedly diminished or absent pulmonary second sound. The fluoroscopic examination revealed a prominent active pulmonary conus and enlargement of the right ventricle in all patients. The 3 patients with atrial septal defects had increased pulmonary blood flow, and the remainder had relatively clear lung fields. The electrocardiograms showed right axis deviation and right ventricular hypertrophy in all. In general, the degree of right ventricular hypertrophy was most marked in those patients having the highest pressure gradient across the pulmonary valve. Preoperative cardiac catheterization was performed on all patients. The pull-back pressure records were considered typical of valvular stenosis, and operation was advised if the right ventricular pressure was 100 mm. Hg or more.

Auricular Septal Defect.—Sixteen patients have had closure of auricular septal defects by the open technique under hypothermia. These are in addition to the 3 patients classified under pulmonary valvular stenosis, who had atrial septal defects closed at the time of pulmonary valvulotomy, and the patient who had correction of anomalous pulmonary venous drainage. One of the 16 had an associated significant pulmonary stenosis and correction of both defects. Twelve patients were in the pediatric age range, between 5 and 14 years, and 4 were adults of 23, 31, 33, and 38 years of age. All patients had significant symptoms; those of pediatric age have had growth retardation, many have had fatigability with exertional dyspnea, frequent lower respiratory infections, and intermittent cyanosis with exertion or during respiratory infections. The physical findings conformed well with those described by Taussig.[6] In general, they have been of asthenic habitus and have appeared underdeveloped and undernourished. None of the patients was cyanotic at rest. Eight, or 50 per cent, had precordial prominence. The only patient with a significant precordial thrill had an associated pulmonary valvular stenosis. The systolic murmur varied from a Grade 1 to a Grade 3 of medium pitch, and usually was heard best from the second to the fourth interspaces at the left sternal border and transmitted to the back. Six of 16 had soft mid-diastolic murmurs along the left sternal border.

Fluoroscopy revealed significant cardiomegaly in all 16 patients except the 1 with pulmonary stenosis. All patients had a prominent right atrial shadow and enlargement of the right ventricle; all had an enlarged full pulmonary conus with increased pulmonary vascularity and intrinsic arterial pulsations. There was no evidence of an enlarged left atrium or left ventricle in any patient. The electrocardiographic findings were as follows: 11 had right axis deviation, 4 a normal axis, and 1 a left axis deviation. Only 4 patients had clear-cut electrocardiographic evidence of right ventricular hypertrophy; 3 of these had right ventricular hypertension of 67 mm. Hg, 55 mm. Hg, and 58 mm. Hg, respectively, and the fourth had an associated pulmonic stenosis with a right ventricular pressure of 75 mm. Hg. All others had a focal bundle branch block over the right precordium, a so-called rsR′ pattern. Ten patients had prolongation of the P-R interval, and 1 had first degree heart block. Five patients had prominence of the P wave as evidence of right atrial dilatation. No patient had evidence of left ventricular hypertrophy.

Preoperative cardiac catheterization was performed on all patients, and all had a significant left-to-right shunt at the atrial level, varying from 1 L./min./M.^{2} to 12.7 L./min./M.^{2} No patient had evidence of a right-to-left shunt or arterial unsaturation; no patient had evidence of a subauricular shunt.

Indication for operation has been the combination of (1) significant symptomatology, (2) cardiomegaly, and (3) a left-to-right shunt exceeding 1.5 L./min./M.^{2} The 1 patient operated on who had a 1 L./min./M.^{2} shunt had, in addition to the atrial septal defect, definite pulmonary valvular stenosis.

TECHNIQUE OF SURGICAL PROCEDURE UNDER HYPOTHERMIA

The operative technique is essentially the same as we have described previously,[7] and is similar to that described by others.[3, 4, 5] It includes perfusion of the coronary circulation with warm, heparinized oxygenated blood during the period of inflow-tract occlusion. Following induction of anesthesia and insertion of an endotracheal tube, the patient is surface cooled in a tub of ice water to a rectal temperature of about 32.5° C. and placed on the operating table over the warming blanket (Therm-o-rite*). The blanket is usually used to prevent excessive downward temperature drift rather than for further cooling, and we prefer to do the intracardiac procedure at a rectal temperature of about 30° C. and preferably when the temperature is beginning to rise. An anterior bilateral thoracotomy has been used most frequently, entering the right chest through the fourth interspace and the left through the third, with division of the sternum by V osteotomy. Recently, pulmonary valvulotomies have been performed by a longitudinal sternal splitting incision, and atrial septal closures have been performed through a right thoracotomy. The pericardium is widely opened, and the venae cavae are dissected free

*Therm-o-rite Products Company, Buffalo, New York.

within the pericardium so that tapes may be passed about them for inflow occlusion. Entrance into the heart or pulmonary artery is gained as follows: The venae cavae are occluded and, after allowing about 20 seconds for cardiac emptying, the pulmonary artery and aorta are occluded with a Satinsky clamp placed through the transverse cardiac sinus. A curved needle (Fig. 1) is placed in the aorta between the clamp and the aortic valve for coronary perfusion. The atrium or pulmonary artery is then opened between previously placed stay sutures. Egress from the heart is accomplished by flooding the atrium or pulmonary artery with saline and applying a nonerushing clamp to the walls. Immediately thereafter, the aortic clamp and the superior vena cava is released. If heart action is satisfactory, the inferior vena cava is next opened.

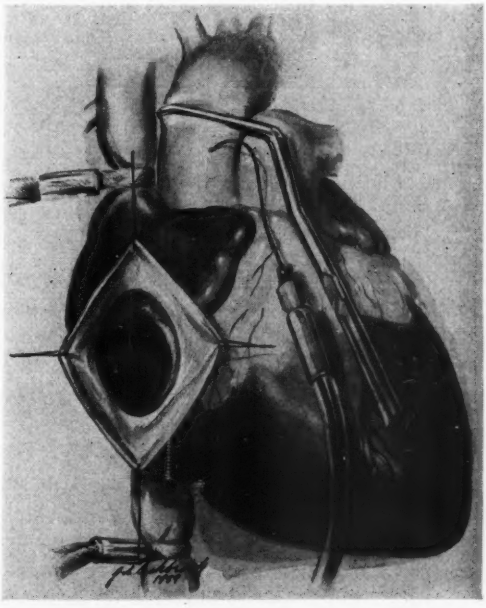

Fig. 1.—The technique of coronary perfusion and the exposure for closure of atrial septal defects.

Coronary Artery Perfusion During Inflow-Tract Occlusion.—We consider this to be a very important adjunct to intracardiac surgery under hypothermia. Coronary perfusion has been discussed by Spencer,[4] Mahoney,[7] Riberi,[8] and others, and its value in the experimental animal has been reported from this laboratory.[9, 10] The details of the experimental study have been reported elsewhere but, in brief, the results were as follows: during inflow-tract occlusion, the pH of coronary sinus blood decreases, and the lactic acid content increases, indicating a rapidly developing myocardial acidosis. If coronary perfusion with warm, oxygenated heparinized whole blood is then begun, the

pH of coronary sinus blood returns to normal, and the lactic acid content returns to pre-occlusion levels (Fig. 2). If coronary artery perfusion is started at the outset of inflow-tract occlusion, the pH of coronary sinus blood and lactic acid content is maintained at pre-occlusion levels (Fig. 3).

Oxygenated blood for coronary perfusion for the earlier cases was obtained by warming the arm of a donor and drawing venous blood in heparin.[11] We encountered considerable variation in the oxygen saturation of the blood obtained in this manner; therefore, we have abandoned this method in favor of a technique of so-called "coronary autoperfusion." Fresh heparinized

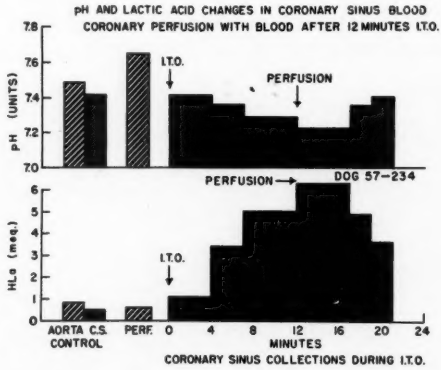

Fig. 2.—Inflow-tract occlusion with coronary artery perfusion.

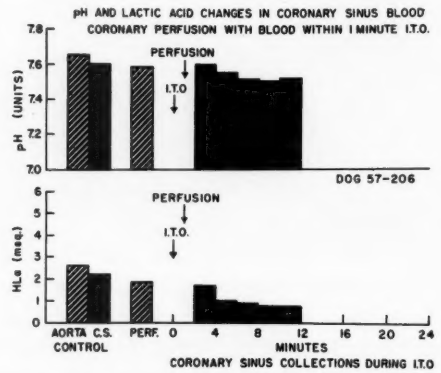

Fig. 3.—Inflow-tract occlusion with coronary artery perfusion.

venous blood is drawn from donors the morning of the operation and infused into the patient's vein, while an equal amount of arterial blood is taken from the patient's aorta by direct needle puncture after the chest has been opened. Thus, complete oxygen saturation of the blood for coronary perfusion is assured. The volume of coronary perfusion during pulmonary valvulotomy has varied from 100 to 400 c.c., and the mean average was 1.9 c.c./min./Kg.; for

closure of atrial septal defects, it varied from 175 to 500 c.c., with an average of 1.5 c.c./min./Kg. The period of inflow-tract occlusion for pulmonary valvulotomy has been between 3 and 4 minutes, and for atrial septal defects usually between 5 minutes and 7 minutes, the longest being 13 minutes.

The operative findings in pulmonary valvular stenosis were characterized by an enlarged muscular right ventricle and post-stenotic dilatation of the pulmonary artery at the point where the jet of blood through the stenotic valve impinged upon its wall.[12] The valvular stenosis was most often due to a funnel-shaped, cone-like fusion of the valve leaflets. The cone might be quite long with thin walls (Fig. 4) or short and thickened at its tip. The opening was usually only 2 to 3 mm. in diameter. The commissures are not as clearly defined in congenital pulmonary valvular stenosis as they are in aortic valvular stenosis, but they can at times be defined and the cuts made accurately in the commissures. Usually two cuts were made converting to a bicuspid valve, but we have the clinical impression that less insufficiency may result if three cuts are made (Fig. 5). The tip of the cone has been excised if it shows fibrous thickening. Three patients presented a flattened fibrous diaphragm; and in 1, two tiny openings were present (Fig. 6). Blount[13] has stated that the thickened fibrous valves occurred in older patients, but this has not been a uniform finding in our patients as this thickening occurred in younger individuals with a very high degree of stenosis.

The most common type of atrial septal defect encountered has been the secundum defect of the septum primum[14]; or as designated by Swan,[2] a foramen ovale defect due to a defect in the valvular foraminis ovalis or complete absence of the valvula. The high defects of the septum secundum usually have no cephalic margins, and are most frequently associated with anomalous pulmonary venous drainage. All of these defects have an adequate margin of septum caudally, and we have purposefully avoided repair of primum defects of the septum primum or endocardial cushion defects by the hypothermic technique. The technique of closure is similar to that described by others.[3, 5] After careful inspection of the atrial cavity, and after locating the site of entrance of pulmonary veins, the venae cavae, and coronary sinus, stay sutures of No. 3-0 silk are placed at either end of the defect and tied, thus converting the oval defect to a slit. The cephalad suture is then continued caudally as an over-and-over stitch, finally tied to the caudal stay after the left atrium has been allowed to fill with blood. Several interrupted sutures are usually inserted for reinforcement. The correction of anomalous pulmonary veins is usually readily accomplished by suturing the ventral margin of the septum to the right of the entrance of the pulmonary veins, thus creating a larger left atrium. It may be impossible to divert pulmonary veins entering high in the vena cava. Following closure of the defect, the right atrium is allowed to fill with blood and is usually flooded with saline before applying a noncrushing clamp to the atrial wall. The right atrium is closed with a continuous suture.

Fig. 4.

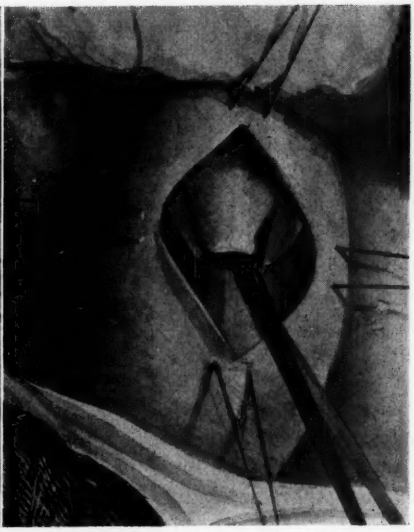

Fig. 5.

Fig. 4.—Exposure for pulmonary valvulotomy.
Fig. 5.—Technique of pulmonary valvulotomy.

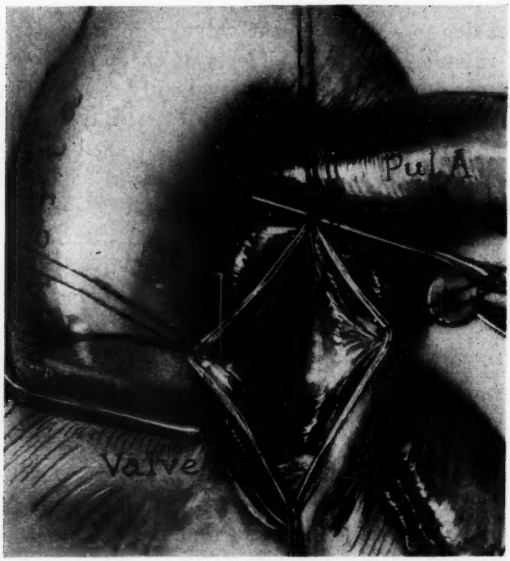

Fig. 6.—Diaphragm type of pulmonary valvular stenosis.

Patients having both pulmonary stenosis and atrial septal defect have had both abnormalities corrected at the same operation. The valvulotomy is performed first, and the circulation is re-established for about 20 minutes to allow cardiac recovery. The atrial septal defect is then repaired during a second period of inflow-tract occlusion.

OPERATIVE COMPLICATIONS

Pulmonary Valvular Stenosis.—There have been no operative or postoperative deaths. One patient, a 33-year-old man, developed ventricular fibrillation which was successfully converted to sinus rhythm. Twenty-one months previously, he had had a transventricular[15] pulmonary valvulotomy performed with a minimal decrease in right ventricular pressure. Coronary artery perfusion was not used and, after 6 minutes of inflow-tract occlusion, ventricular fibrillation developed when the inferior vena cava was opened. Cardiac arrest was induced by re-establishing inflow-tract occlusion and, after cross-clamping the aorta, 19 c.c. potassium chloride solution (1 mEq./c.c.) was injected into the coronary circulation. Circulation was maintained by massage and, after 3 minutes, the heart became responsive and 20 c.c. of 50 per cent glucose was injected intravenously. This was followed by a spontaneous effective ventricular beat and soon thereafter a sinus rhythm (method described by Mavor and his associates[16, 17]). The patient's postoperative course was uneventful. There were no other operative complications in this group of patients.

Atrial Septal Defects.—There was one operative death due to ventricular fibrillation, and 2 other patients developed this operative complication, but it was successfully converted with potassium and glucose. The first patient in this series did not have coronary perfusion during 5 minutes of inflow-tract occlusion, and fibrillation began while the atrium was being closed. Patients 6 and 8 had coronary perfusion with blood from a "warmed donor arm" and, in both instances, the perfusate was desaturated. Patient 6, a 6-year-old girl, began to fibrillate while the defect was being closed. The closure was completed, and defibrillation was successfully accomplished with potassium and glucose. Technical difficulties were encountered in Patient 8 which required 13 minutes of inflow-tract occlusion. Fibrillation began 3 minutes after circulation was restored, and attempts at conversion were unsuccessful in spite of both electrical shock and administration of potassium with glucose. No ventricular arrhythmias occurred when coronary perfusion was carried out with fully saturated arterial blood. Six patients had atrial fibrillation during some period of cardiac manipulation, but this caused no difficulty and reverted spontaneously.

POSTOPERATIVE COMPLICATIONS

The patients in both groups required only the usual postoperative support necessary for any thoracotomy. No problems of either postoperative bleeding or thrombosis were encountered and, in general, the postoperative

period was remarkably benign. One patient developed an unsuspected psychiatric difficulty after doing well in the postoperative period. She subsequently died of pneumonia, and is the one late death in the series.

CLINICAL RESULTS

Pulmonary Valvulotomy.—These patients have been followed for a varying period of from 2 months to 42 months. Those who have been followed for more than 6 months have all become asymptomatic. The 1 patient who had frank cardiac failure before operation is now 17 months postoperative, and has no evidence of failure, does not require digitalis, and is able to work full time. The clinical course, the electrocardiogram, and pulmonary valve pressure gradient data are tabulated in Table I. All patients have shown

TABLE I. CLINICAL RESULTS—VALVULAR PULMONIC STENOSIS
(THE SEVERITY OF CLINICAL SYMPTOMS AND THE RIGHT VENTRICULAR HYPERTROPHY AS TABULATED ON A BASIS OF 0 TO 4+)

PATIENT	AGE AT OPERATION (YEARS)	LENGTH OF FOLLOW-UP (MO.)	CLINICAL COURSE		ELECTROCARDIOGRAM		RV—P. ART. SYSTOLIC GRADIENT (MM. Hg)	
			PRE	POST	PRE	POST	PRE	POST
1. R. W.	13	42	2+	0	3+ RVH	Normal	150	15
2. R. T.	7	40	4+	0	4+ RVH	Normal	167	14
3. R. G.	33	37	1+	0	3+ RVH	1+ RVH	106	—
4. W. S.	14	36	2+	0	4+ RVH	1+ RVH	153	10
5. K. K.	11	34	1+	0	2+ RVH	Normal	91	7
6. G. B.	36	31	1+	0	2+ RVH	1+ RVH	140	19
7. R. D.	6	28	2+	0	3+ RVH	Normal	164	24*
8. R. W.	6	26	2+	0	2+ RVH	Normal	110	10
9. C. F.	7	24	1+	0	3+ RVH	Normal	125	15
10. D. K.	19	23	2+	0	2+ RVH	Normal	97	—
11. C. W.	5	21	2+	0	4+ RVH	Normal	173	11
12. D. M.†	6	18	1+	0	2+ RVH	Normal	85	16
13. J. F.	12	17	1+	0	3+ RVH	Normal	102	9
14. C. O.	30	17	2+	0	3+ RVH	1+ RVH	200	10*
15. J. D.†	7	16	1+	0	3+ RVH	Normal	105	25
16. N. H.	6	15	1+	0	2+ RVH	Normal	100	16
17. M. G.†	6	10	2+	0	2+ RVH	Normal	100	16
18. D. B.	37	3	1+	0	2+ RVH	1+ RVH	66	9*
19. J. D.	5	2	2+	0	3+ RVH	1+ RVH	165	62*

*Operating room pressure recording.
†Associated auricular septal defect.

significant reduction of right ventricular hypertrophy by electrocardiogram, 13 actually have no residual right ventricular hypertrophy 10 months to 2 years following operation, and 4 patients maintain 1+ right ventricular hypertrophy at 17 months to 37 months.

The pressure gradient across the pulmonary valve has been determined by preoperative catheterization, before and immediately after valvulotomy in the operating room, and by catheterization 1 year postoperatively. The first 5 patients operated on by the open technique had an immediate reduction in the right ventricular pressure to near normal levels at operation. The sixth patient had a minimal reduction in spite of what had impressed us as

a typical valvular obstruction and a satisfactory valvulotomy. At that time, we were fearful that an associated infundibular stenosis had been missed. The immediate postoperative gradient was 150 mm. Hg, but catheterization 1 year later revealed a gradient of only 10 mm. Hg. This situation has been encountered in 6 patients (Fig. 7), and all have had a satisfactory reduction in the pulmonary valve gradient when studied 6 months to 1 year later.[18] The data on patients having immediate regression of the gradient are compared with those having late regression (Fig. 8), and the end result is the same with near normal pressure relations between the right ventricle and

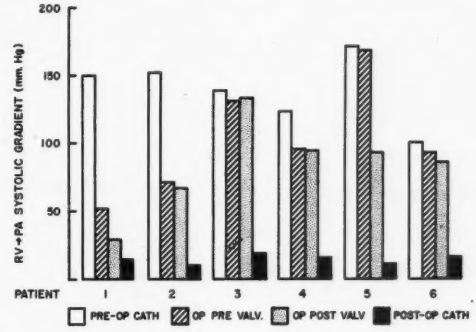

Fig. 7.—Late regression of right ventricular pulmonary artery pressure gradient in patients having hypertrophy of the right ventricular outflow tract.

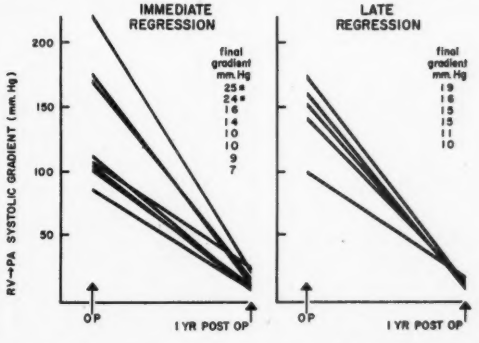

Fig. 8.—Right ventricular pulmonary artery pressure gradients following valvulotomy.

pulmonary artery. The patients having the gradual decrease in right ventricular pressure have also had a slower regression of electrocardiographic evidence of right ventricular hypertrophy.

Reversible Outflow Tract Hypertrophy of the Right Ventricle.—Fig. 9 shows the normal outflow tract of the right ventricle portrayed by the cinefluorographic technique of angiocardiography.[19] View *A* shows the outflow tract at the end of systole, and *D* early in systole. Fig. 10 is the same view of

the outflow tract in a patient with pulmonary valvular stenosis exposed at comparable times during systolic ejection of the radiopaque material. During late systole, the hypertrophied infundibulum causes marked narrowing of the outflow tract, but it does expand during maximum systolic ejection. Those patients who do not have an immediate reduction in right ventricular pressure

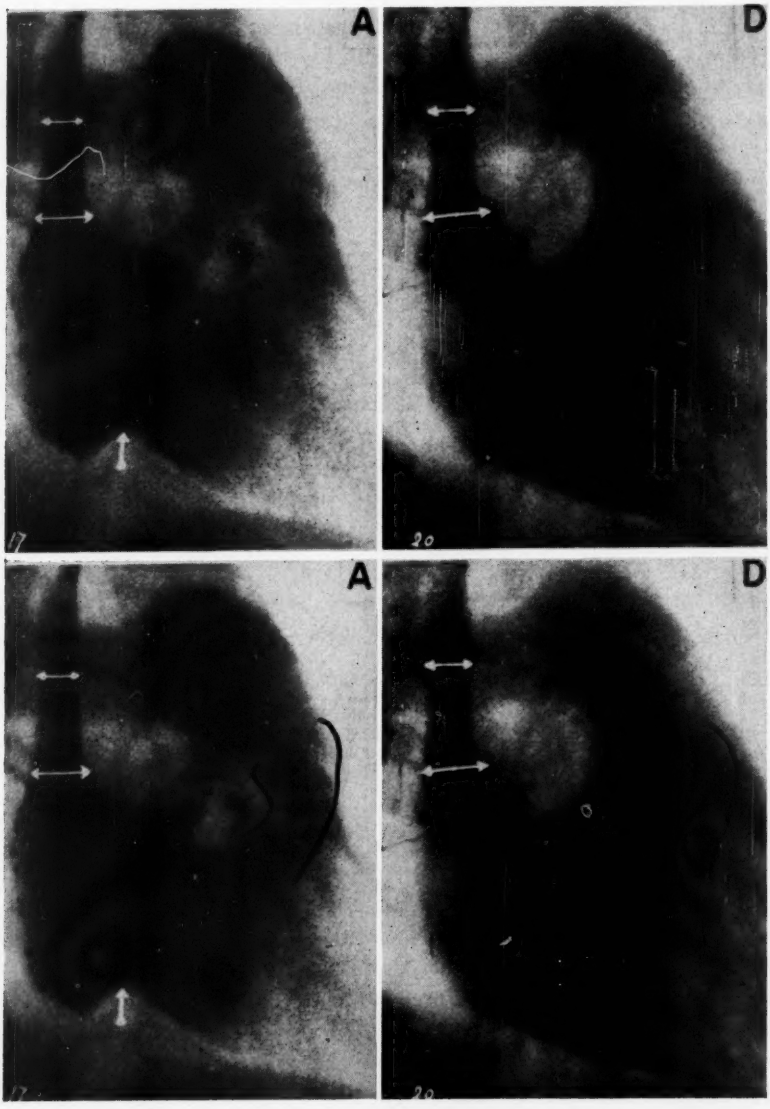

Fig. 9.—Cine-angiocardiogram showing normal outflow tract of right ventricle.

after valvulotomy have a markedly contractile muscular and hypertrophied infundibulum. If the operator's finger is inserted through the valve, into the outflow tract, a very firm contraction is noted during systole. This differs, however, from a true infundibular stenosis in that there is no fixed fibrous band or inexpansile area of outflow obstruction.

Atrial Septal Defects.—None of the surviving 14 patients has had postoperative symptoms (Table II). All have had marked reduction in the cardiothoracic ratio 1 year following operation. Fluoroscopic examination indicates

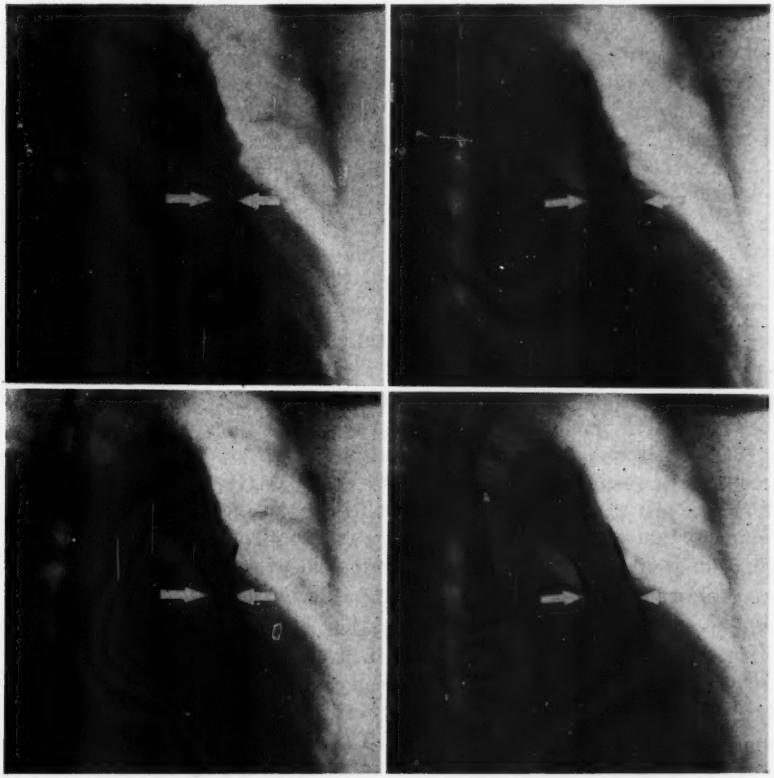

Fig. 10.—Cine-angiocardiogram showing right ventricle outflow tract in patient with pulmonary valvular stenosis.

a return to normal pulmonary vascularity. Nine patients who have had postoperative catheterization had complete closure of the defect, with no evidence of a left-to-right shunt and no right heart hypertension. Those not yet catheterized have had a rapid increase in growth and development and a marked decrease in physical findings, although a soft murmur may still persist, even though the defect is completely closed. One 12-year-old girl has

gained 15 pounds since operation, has no symptoms, and has had a significant decrease in heart size. She does, however, have a hyperactive precordium and some residual increase in pulmonary vascularity, so there may still be a small residual left-to-right shunt.

TABLE II. CLINICAL RESULTS—AURICULAR SEPTAL DEFECTS

PATIENT	AGE AT OPERATION (YEARS)	LENGTH OF FOLLOW-UP (MO.)	CLINICAL COURSE		CARDIO-THORACIC RATIO		LEFT-TO-RIGHT SHUNT (L./MIN./M.^{2})	
			PRE	POST	PRE	POST	PRE	POST
1. M. A.	14	32	2+	0	.55	.45	4.5	0
2. C. M.	5	28	3+	0	.60	.48	3.5	0
3. L. D.*	12	28	2+	0	.45	.40	1.0	0
4. J. D.	5	28	2+	0	.58	.50	2.3	0
5. R. W.	31	22	2+	0	.52	.50	12.7	—
6. D. L.	6	21	2+	0	.55	.45	3.5	0
7. J. S.	6	20	2+	0	.60	.48	3.2	0
8. M. F.	12	Operative death	2+	—	.55	—	6.2	—
9. W. R.	12	18	3+	0	.58	.52	5.5	
10. D. R.	13	16	1+	0	.54	.45	2.3	0
11. C. W.	23	12	2+	0	.50	.48	5.3	0
12. S. M.	10	12	2+	0	.50	.48	2.9	
13. M. S.	38	3 wk. postop. death	2+	—	.50	—	5.5	—
14. E. V.	7	9	3+	0	.55	.50	5.0	
15. R. H.	9	6	2+	0	.55	.49	8.5	
16. E. A.	33	4	2+	0	.52	—	—	

*Associated pulmonic stenosis.

DISCUSSION

The hypertrophy of the right ventricular outflow tract, which has been observed in association with pulmonary valvular stenosis, presents an interesting problem. When we first found little or no decrease in the right ventricular pressure following an adequate valvulotomy, we presumed that an infundibular obstruction had been overlooked even though such an obstruction could not be defined by finger palpation. The patient had a favorable clinical course, and cardiac catheterization 1 year later revealed a marked fall in right ventricular pressure and a minimal gradient across the pulmonary valve. Five other patients have had well-documented evidence of gradually decreasing pressure gradients following valvulotomy. The angiocardiograms and the clinical course of these patients indicate that a physiological hypertrophy of the outflow tract may develop as the result of purely valvular stenosis and that, after the valvular obstruction is overcome, the hypertrophy regresses.

The combination of pulmonary valvular stenosis and infundibular stenosis coexisting in the presence of an intact ventricular septum has been discussed by numerous authors. McGoon and Kirklin[20] estimated that the two are associated in about 25 per cent of the cases, and they found infundibular stenosis more often present in older children and adults with valvular stenosis. Gadboys[21] had 6 patients who required infundibular resection in conjunction

with valvulotomy. Certainly, the presence of pure infundibular stenosis without a ventricular septal defect and without pulmonary valvular stenosis is quite rare. Our experience has indicated that muscular hypertrophy can simulate an infundibular obstruction, but that it is possible to differentiate the two preoperatively and at the operating table. Needless resection of the wall of the outflow tract can thus be avoided.

The results of pulmonary valvulotomy by an open technique appear superior to the results obtained by the closed transventricular technique. Blount[13] estimated an over-all mortality rate of 10 per cent of operations by the transventricular route reported in the literature and a 5 per cent mortality by the open technique. There have been no fatalities in the group reported here, but the total number of operations is not large. The right ventricular pressure usually regresses to a near normal level after open valvulotomy, and the gradient across the pulmonary valve is usually less than 20 mm. Hg. The average right ventricular pressure in this series is 33 mm. Hg, with an average gradient of 14 mm. Hg. One possible disadvantage of the open technique is the danger of pulmonary valvular insufficiency.[22] Five patients have postoperative diastolic murmurs along the left sternal border, and 1 patient has hemodynamic evidence of pulmonary insufficiency with a pulmonary artery pressure of 29/2 mm. Hg. No patients have evidence of clinical problems secondary to this, nor have they developed electrocardiographic evidence of right ventricular hypertrophy or of increase in heart size. Many years of observation will be necessary to evaluate this aspect of the problem.

Our clinical experience confirms the value of coronary artery perfusion with oxygenated whole blood. The amount of whole blood used for perfusion is less than normal coronary blood flow; but at reduced temperatures, the low flow rate is adequate to prevent myocardial anoxia and acidosis in the experimental animal and in the human patient. During inflow-tract occlusion without perfusion, the heart rate gradually slows, and the myocardium becomes cyanotic. The electrocardiogram deteriorates, and frequently the heart requires massage when circulation is re-established. This is undoubtedly the most dangerous period from the standpoint of ventricular fibrillation. In contrast with this, during coronary perfusion, the myocardium remains pink, the rhythm is regular, and the electrocardiographic changes are minimal. When circulation is restored, the heart action is usually vigorous, and the systemic arterial pressure is maintained at the pre-occlusion level of that degree of hypothermia. The beneficial effect of the neostigmine used by Swan[2] is, in part, due to a slowing of the heart and, thus, a reduction in metabolic demands of the myocardium.

The most obvious disadvantage of the open heart procedures performed under hypothermia is the limitation in time available for intracardiac manipulation. The method should be limited to the procedures described, plus possibly open valvulotomy for congenital aortic stenosis, although cardiac bypass is probably preferable for this. Preoperative diagnosis must be accurate;

and, if there is any question of a complicated lesion requiring intracardiac correction, the technique should not be used. One of our patients who had both a pulmonary valvulotomy and closure of an atrial defect has postoperative evidence of a small ventricular septal defect which was not evident on preoperative studies, and which might have been found if cardiac bypass had been used.

It should be emphasized that the successful use of hypothermia requires careful attention to many details, but it is simpler than cardiopulmonary bypass techniques and it requires much less blood, manpower, and equipment. Our own experience persuades us to continue its use for the simpler procedures and, although readily available, to reserve the pump-oxygenator for the more complicated defects. Perhaps the greatest value of hypothermia in cardiac surgery will be its use in combination with cardiopulmonary bypass.

SUMMARY

A review of the experience with 35 patients upon whom cardiac surgery was performed with the aid of hypothermia is presented. Nineteen patients underwent pulmonary valvulotomy, and 16 had closure of atrial septal defects by open technique. The physical findings and indications for operation are presented for each of these 2 groups of patients. The technique for surgical correction of the lesions, including the application of coronary artery perfusion during inflow-tract occlusion, is outlined. The clinical results are evaluated both in the immediate postoperative period and after long-term follow-up. Catheterization data are presented, and particular attention is directed to the reversibility of the outflow-tract hypertrophy of the right ventricle associated with valvular pulmonic stenosis.

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DISCUSSION

DR. JULIAN JOHNSON, Philadelphia, Pa.—I would like to emphasize again the value of intermittent occlusion under hypothermia. If you get in a spot where you can't complete your suture within the 5 or 6 minutes which you have allotted yourself, there is no reason why you can't back out, let the heart recover, and then go back in at a second period.

We have used this successfully. We have limited our hypothermia to 90° F. and have not had inflow occlusion for more than 4 or 5 minutes. Even without coronary perfusion we have had virtually no difficulty under these circumstances. We have set 4 minutes as our goal, but if we find that we can complete our suture within another half minute or so we are apt to go ahead and finish. But if it is apparent that we are going to take more than 4½ or 5 minutes, we stop, take the clamps off, let the blood run through the heart for 10 minutes, and then go back for a second period. We have had virtually no difficulty with this since we have put these limitations on ourselves.

Previously when we would get in a tight spot and maybe take 8 or 9 minutes in one period of occlusion we did have trouble.

DR. SAFUH ATTAR, Baltimore, Md.—We have used deep hypothermia to a lower degree than has been used in this presentation. We have brought our patients down to 26° C. and so far we have not had any untoward effect in the sense of frequent ventricular fibrillations in which we could not revert the rhythm back to normal.

However, we have had unusual complications, and this is the reason for my coming up here, to inquire whether you have had similar ones. We used this technique for the correction of pulmonary stenosis and atrial septal defects in the same situations as stated by the authors. However, we encountered the complication of peroneal palsy in 3 cases. This was detected immediately after the operation and had to be treated in the usual manner. There was no definite evidence of any pressure on the peroneal nerve as the hypothermia was being used.

I would like to address the question whether the deep hypothermia of the nerve, since we brought the temperature down to 26° C., could have caused the peroneal palsy.

DR. MAHONEY (Closing).—I would like to thank the gentlemen who discussed and asked questions with regard to the paper.

So far as Dr. Johnson's intermittent occlusion is concerned, we have used this, of course, ourselves. We feel that we can be allowed between 7 and 8 minutes of occlusion time, using coronary perfusion with the oxygenated whole blood. But on numerous occasions we have had to do intermittent occlusion and we feel it is a very worth-while thing to do. Of course we do it when doing both a pulmonary valvulotomy and an atrial septal defect on the same patient.

In regard to the second discusser's questions, our temperatures are as a rule between 30° and 31° C. rectal at the time of the inflow tract occlusion. We have not had any nerve palsies as a result of hypothermia to our knowledge. I doubt very much whether the hypothermia itself had to do with the peroneal palsy, although I am not sure.

I would like to emphasize that one must pad these patients extremely well and be very careful about pressure points, else one gets into severe difficulties as a result of the cold, particularly if one is using a blanket.

SIMPLIFIED TECHNIQUE FOR DIRECT VISION PULMONARY VALVOTOMY

Conrad R. Lam, M.D., and Rodman E. Taber, M.D., Detroit, Mich.

THERE is general agreement at the present time that if the surgeon is to make the best possible correction of pulmonic valve stenosis, he must be able to see what he is doing. This principle, however, has been given reluctant acceptance by some surgeons, including the senior author,[1, 2] because the transventricular method popularized about 10 years ago by Brock[3, 4] had many attractive features. First of all, it was the only operation available at that time as an alternative to the shunt operations which were soon found to be contraindicated in pulmonic stenosis with intact ventricular septum.[5, 6] It could be performed rapidly; if necessary, the valve of a dying, cyanotic infant could be opened within 10 minutes of the time of the skin incision. The mortality of the operation was low. In the series of 75 patients operated upon at the Henry Ford Hospital before June 1, 1957 (when our present method was adopted as a routine procedure), there were only three deaths and one of these was in an infant only a week old.

The immediate clinical results of the transventricular operation appeared to be satisfactory. For example, the first patient in our series, operated upon in May, 1950, showed immediate reduction in heart size and was in good health 8 years later. The second patient had a right ventricular pressure of 70 mm. Hg before the operation; 6 months later it was down to 30 mm. Hg. Clinical examination of this patient 7 years later revealed a normal heart size.

The technical aspects of the operation were made easier by the introduction of new instruments, notably the adjustable valvulotome of Potts and his associates,[7] and the modification of the Bailey mitral valve guillotines, which were especially useful in adult patients.[8]

However, as early as the 1953 meeting of this Association, several members rose to point out that the transventricular operation was not uniformly satisfactory.[9, 10] In a considerable number of cases, postoperative catheterization of the right heart had shown that right ventricular pressures were not sufficiently reduced or an immediate reduction had not been permanent.[12] At this meeting, Dodrill[9] reported a successful case of open pulmonic valvotomy, in an operation utilizing right heart bypass and autogenous lung oxygenation.

From the Division of Thoracic Surgery of the Henry Ford Hospital, Detroit, Mich.
Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

Swan[11] had already begun to use hypothermia to permit a safe period of vena caval occlusion for open valvotomy, and his first cases were reported in detail at the next meeting of the Association,[13] and elsewhere.[14]

Eventually, follow-up studies of our own series began to reveal certain unsatisfactory results. For example, the sixth patient in our series, operated upon originally at the age of 4, was found to have a right ventricular pressure of 140/0 mm. Hg 8 years later. A recent survey of the transventricular group reveals that 10 patients have had a second valvotomy by an open technique and it is not unlikely that an equal number will have a second operation in the near future. This unsatisfactory record naturally aroused our interest in open valvotomy, and a few patients were operated upon under hypothermia. However, on June 10, 1957, we had an experience which led us to adopt the simplified method of pulmonary valvotomy, without hypothermia, which is being reported today.

A 46-year-old woman was found to have the combination of atrial septal defect with pulmonic stenosis. The right ventricular pressure was 80/4 mm. Hg and the pulmonary artery pressure was 24/10. In order that the pulmonary valvotomy could be done by the Brock method and the atrial septal defect closed by the two-pointed needle technique, a transverse incision, crossing the sternum at the third interspaces, was made. An adjustable valvulotome was introduced into the ventricle and through the valve. A slight cutting sensation was noted, but measurement of the pressures in the ventricle and pulmonary artery showed that the gradient had not been changed. Before doing anything further about the valve, the small atrial septal defect was closed. We then returned to the problem of the pulmonary valve and employed a technique which, with minor modifications, has now been used in 48 other patients with isolated pulmonary valvular stenosis.

TECHNIQUE

We have almost invariably used a transverse incision (Fig. 1) because of the cosmetic advantage and the excellent exposure provided for visualization of the heart, for snaring of the venae cavae, and for the valvotomy itself. The submammary incision exposes the pectoral muscles which are divided to expose the third interspace on the right and the third or second interspace on the left. The internal mammary vessels on the right side are divided between ligatures, after which the sternum is transected and the internal mammary vessels on the left are divided. It is not necessary to open the pleural space on the left, but, if this is done inadvertently, tube drainage does not have to be provided for this side. The pericardial incision consists of a horizontal portion with extensions upward over the pulmonary artery to the pericardial reflection and downward near the right phrenic nerve almost to the diaphragm to expose the inferior vena cava. Tapes are passed around the two venae cavae to serve as occlusion snares. The pulmonary artery and aorta are not separated, since no distal clamp is to be applied to the pulmonary

artery. There is no reason to put on such a clamp, since there is no back pressure in the lung to cause retrograde flow and no aspirating action which might cause air to be taken in.

Traction sutures are placed with an atraumatic needle at the proximal and distal ends of the proposed incision into the pulmonary artery. An atraumatic type of clamp is then placed longitudinally to exclude the portion of the artery for the incision. This maneuver is facilitated by the post-stenotic dilatation which almost invariably accompanies pulmonic valve stenosis. The artery is incised and additional traction sutures are placed to retract the two lips of the incision. The vena caval snares are tightened and the anesthetist is asked to give notification of the passage of 1 minute of time.

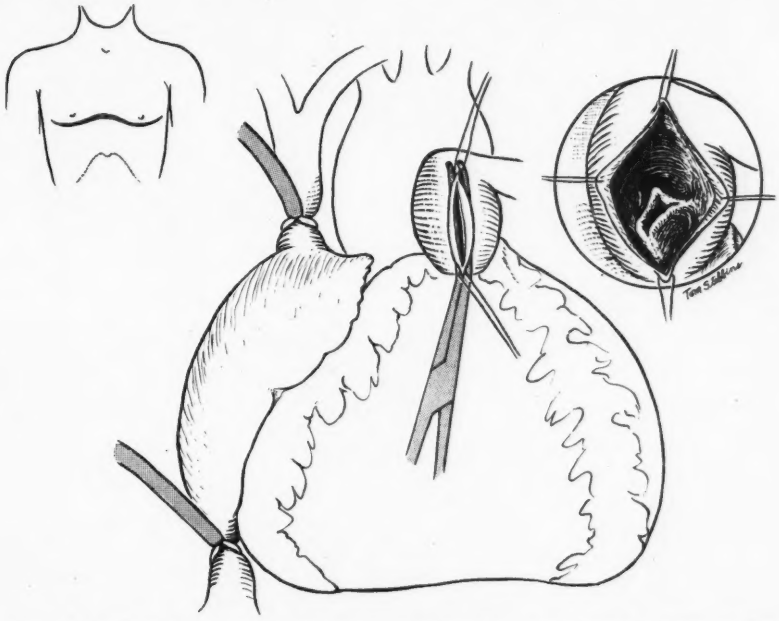

Fig. 1.—Method of exposure of the pulmonary valve for direct vision valvotomy without hypothermia. Note that no occluding clamp is placed on the pulmonary artery distal to the incision.

Restoration of the circulation after 1 minute is considered to be desirable, and, after 2 minutes, mandatory. The maximum period of occlusion in our series has been 1½ minutes, although obviously the occlusion period may be repeated an indefinite number of times with periods of normal circulation intervening. Following occlusion of the venae cavae, the heart is allowed to beat several times to empty the right side, and the pulmonary artery clamp is removed. An assistant places a vein retractor at the proximal angle of the incision. The blood in the artery is aspirated and, as soon as possible, if the size of the valve orifice permits, the tip of the aspirator is placed in the right ventricle for a few seconds. Note is then made of the type of valve and the

indicated valvotomy performed. If there is no sign of commissures in the typical dome-shaped valve with severe stenosis, incisions are made anteriorly and posteriorly out to the arterial wall (Fig. 2). It is useful to have the first assistant, who stands on the left side of the table, grasp one side of the valve with a forceps while the surgeon holds the other side. If there are actual commissures or rudimentary ones, the incisions are made carefully along the commissural lines. Pulmonic insufficiency is an unnecessary sequel to open pulmonic valvotomy. Finally, a finger is introduced through the opened valve

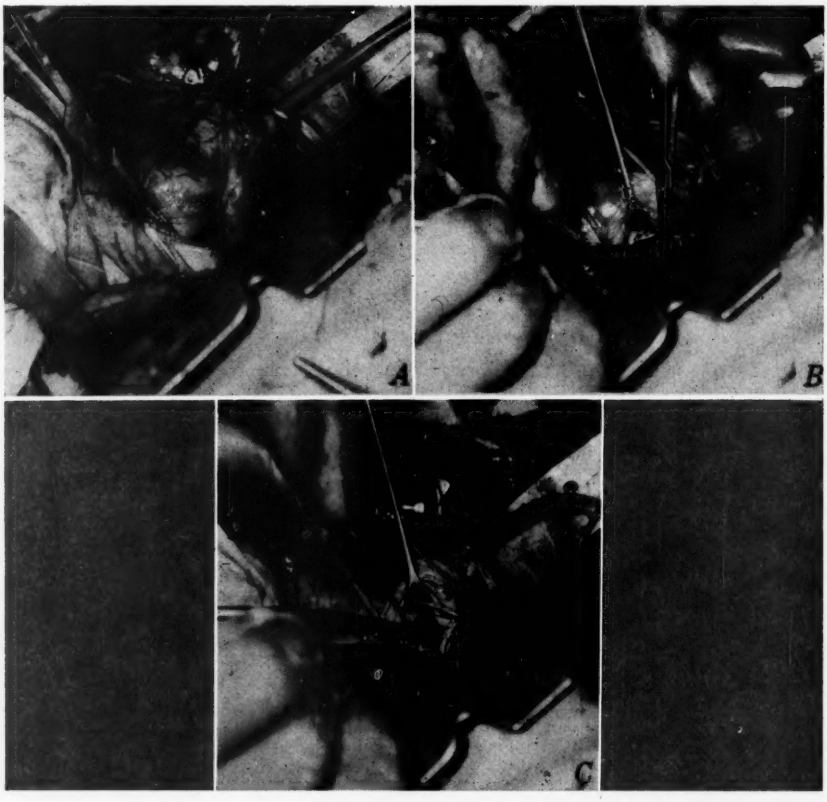

Fig. 2.—Photographs of a typical pulmonary valvotomy. *A*, The artery has been incised in a portion excluded by a longitudinally placed clamp. *B*, Removal of the clamp reveals the dome-shaped deformed valve. *C*, The valve has been opened by anterior and posterior incisions.

into the ventricle to verify the patency of the entire outflow tract. In 1 case, a narrow fibrous band of subvalvular stenosis was noted, and this was cut away during a second period of caval occlusion. It is to the credit of our pediatric diagnostic team (Dr. R. F. Ziegler and Dr. Edward Green) that no instance of infundibular stenosis appeared in patients scheduled for open valvotomy. We consider that the problem in infundibular stenosis with intact ventricular septum is so complicated that cardiopulmonary bypass is indicated.

Following the ventricular exploration, the superior vena caval snare is released and, in a few seconds, blood is ejected from the right ventricle. In the meantime, the lips of the pulmonary artery incision have been held up with the traction sutures and, as the artery fills and overflows with blood, the clamp is closed about the incision. There has been no suggestion of air embolism in our series. The arterial incision is then closed with 5-0 silk, placed as a continuous horizontal mattress type of suture, reinforced by returning with an over-and-over suture, after which the clamp is removed. The pericardium is sutured loosely, the right side of the chest is drained into a water-seal bottle, and the chest is closed in the conventional manner. Only rarely has there been sufficient blood loss or other factors, such as preoperative anemia, to make a transfusion necessary.

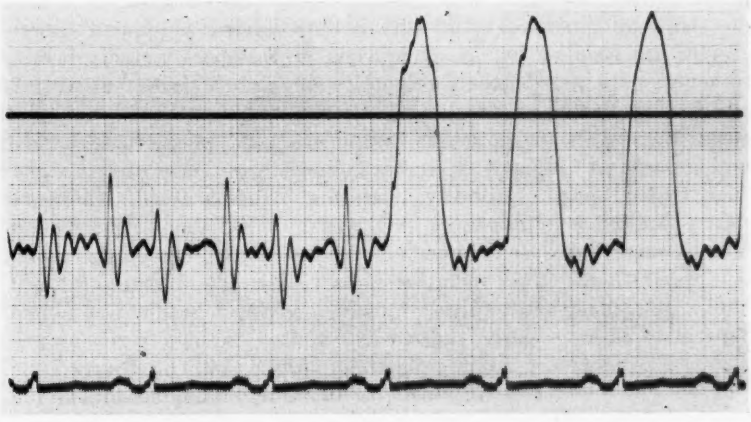

Fig. 3.—Pressure tracing at catheterization of the right heart, showing the typical picture of pure valvular stenosis. The low pressure in the pulmonary artery on the left may be compared with the high pressure of the right ventricle on the right.

RESULTS

Since June, 1957, 49 patients have been scheduled for open pulmonary valvotomy by this technique. In 48 patients, the proposed valvotomy was carried out. There was 1 case in which there had been a gross error in diagnosis and there was no significant pulmonary stenosis; this case will be discussed later. There was a wide age range. Eight patients were between the ages of 1 and 3 years, 27 were from 3 to 10, 4 from 20 to 30 years, and 3 were over thirty. The oldest patient was 47 years of age.

There was one postoperative death; this occurred in the youngest patient in the series, a child 18 months of age. Although the increased risk of operation at this age was appreciated, it was evident that immediate relief of the severe pulmonic stenosis was indicated. The child was first seen at the age of 6 months and was catheterized. The right ventricular pressure was 110/6 mm. Hg and the pulmonary artery could not be entered. Ten months later, a second catheterization showed that the ventricular pressure had risen to 170/0. At open valvotomy, it was found that the valve had a tiny opening

which would barely admit a small aspirator tip. Valvotomy was carried out to produce a bicuspid valve in the usual manner. The finger could not be passed through the valve ring, but a dilator indicated that no localized infundibular stenosis existed. The postoperative course was stormy, with abdominal distention on the first day and difficulties with pulmonary secretions. On the third postoperative day, tracheotomy was done to facilitate the removal of secretions. There was continued respiratory embarrassment and death occurred on the fourth day. Autopsy showed extensive atelectasis and pneumonia. The pulmonary valvotomy appeared to be adequate, but the marked hypertrophy of the entire right ventricle caused some narrowing of the outflow tract. The exact role of this relative obstruction in the fatal issue could not be stated with certainty. We are inclined to believe that when the localized valvular obstruction is relieved, the hypertrophy of the ventricular outflow tract will disappear and with it the tendency to obstruction.

There has been no important problem of postoperative complications in the other 47 patients. In the short period of follow-up observations, clinical studies have indicated an excellent correction of the defect in every patient. In several cases, the murmur has disappeared and in all there has been a reduction in heart size and electrocardiographic evidence of less right ventricular hypertrophy. Naturally, with the experience with the transventricular operation in mind, there may be skepticism about the long-term results until there have been a number of postoperative catheterizations. One patient, aged 47, had a preoperative right ventricular pressure of 100/0 mm. Hg and a pulmonary artery pressure of 35/0, giving a gradient of 65 mm. Hg. Postoperative catheterization showed a reduction of the ventricular pressure to 40/0 and a pulmonary artery pressure of 35/5, a gradient of only 5 mm. Hg.

There was one frank diagnostic error in a patient scheduled for pulmonary valvotomy which resulted in the patient's death. This occurred in a child 18 months of age. There was a systolic murmur over the pulmonary artery suggestive of pulmonic stenosis. Unfortunately, the catheterization data were interpreted as being completely confirmatory for this provisional diagnosis. No shunting at any level was demonstrated; the oxygen saturation in the inferior vena cava was 11.5 vol. per cent; in the superior vena cava, 10.8 vol. per cent; in the right ventricle, 11.2 vol. per cent; and in the pulmonary artery, 11.7 vol. per cent. The pressure in the right ventricle was 90/20-2, and the pulmonary artery pressure was 16/2. In retrospect, there were some danger signals, but these were not noted in time to prevent the fatality.

At operation, it was evident that post-stenotic dilatation of the pulmonary artery was absent. When the exclusion clamp was applied to the pulmonary artery, the heart action rather promptly became poor. It was thought that the clamp was occluding the stenotic valve orifice in some way. Also, it was noted that when the vena caval snares were occluded, there was not good collapse of the right auricle. A second application of the pulmonary artery clamp again resulted in cardiac difficulty. The decision was made to open the artery during caval occlusion without the use of the clamp. Pink blood

came out of the ventricle. The pulmonary valve showed little if any stenosis, although token cuts were made at its commissures. The clamp was replaced and suturing of the vessel was begun. The heart began to fail and the suture line was rapidly completed. Intermittent cardiac compression was begun quickly and this reversed the signs of cerebral anoxia, but the heart never showed any further tendency toward spontaneous beating in spite of an hour and a half of resuscitative efforts. Autopsy showed two atrial septal defects, one of the secundum variety and another of the ostium primum type with minimal deformity of the mitral valve. It was evident that catheterization had not revealed the atrial septal defects because the shunt was balanced. There is no explanation for the error in determination of the gradient between the ventricle and pulmonary artery. Obviously, the patient should have been scheduled for repair of the septal defects with the aid of the pump-oxygenator. Following this unfortunate experience, all of the data, including angiocardiograms, were carefully scrutinized and there were several things to suggest that the diagnosis was not simple pulmonary valve stenosis. The typical post-stenotic dilatation of the pulmonary artery was missing. The lung fields were relatively clear, but were more suggestive of pulmonary resistance than diminished flow. The angiocardiograms did not substantiate the diagnosis of valvular stenosis.

SUMMARY AND CONCLUSIONS

It is proposed that open pulmonary valvotomy without hypothermia and without the pump-oxygenator is feasible and safe. Valvotomies have been carried out in 48 patients with a single mortality, which occurred in the youngest patient in the series. A second fatality occurred in a patient in whom pulmonic stenosis was absent, and in whom, at autopsy, two atrial septal defects were found. The operation is suitable only for pulmonic stenosis of the valvular type. Differentiation of this type from isolated infundibular stenosis and other congenital defects should be possible with the diagnostic techniques available to the cardiovascular team.

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DISCUSSION

DR. HENRY SWAN, II, Denver, Colo.—I would like to compliment Dr. Lam on his usual level of presentation of his material. It is always extremely interesting and vivid, the way Conrad can tell you what he does.

I merely rise to reaffirm our belief and confidence in the use of the open valvuloplasty for the pulmonary valve. We continue to use hypothermia because, unlike Conrad, although I admit the operation usually takes only 1½ or 2 minutes, I like to have 4 or 5 minutes available for a 2-minute operation, so that you don't feel hurried. I agree, though, that one could certainly go back after short occlusions, as Dr. Johnson has suggested and as we have done with arterial septal defects for a number of years.

Now, on the other hand, we continue to use hypothermia because in our opinion and in our practice we believe it does not add risk to the operation. The risk of hypothermia at 30° to 31° C. we feel is roughly equivalent to that of ether anesthesia, and for this reason we do not feel that it adds any risk to the operation of pulmonary valvuloplasty.

We have had experience with something over 60 patients now, and we agree with Dr. Mahoney that there is no evidence that there is actual true infundibular stenosis associated with these patients. You have a hypertrophy of the outflow tract, which does go away as measured over a period of several months, and we have yet to see our first patient who had true infundibular stenosis associated with valvular stenosis.

As we are about to discuss with you in the next paper, we believe that one can very readily handle infundibular stenosis when it occurs as an isolated lesion and, therefore, although it is true that it is nice to be able to distinguish preoperatively, Dr. Lam, between valvular and infundibular stenosis, if you have a patient under hypothermia you are able to manage either condition with equal facility. So that we still believe that it is desirable to have the patient under hypothermia, but we couldn't agree more that the open valvuloplasty is the best approach to this condition.

DR. DONALD B. EFFLER, Cleveland, Ohio.—I, too, would like to congratulate Dr. Lam for his presentation. It appears that the operative time is getting longer—Dr. Lam took 1 minute, Dr. Swan took 4 minutes, and now I propose a method that takes much longer. At the Cleveland Clinic we advocate surgical treatment of valvular pulmonic stenosis utilizing extracorporeal circulation with the pump-oxygenator. Our numerical experience is about the same as that described by Dr. Lam. We use cardiac bypass for several reasons. First of all, we, too, were displeased with the long-term results that followed the closed methods of pulmonary valvulotomy. Second we recognize the possibility of diagnostic error, or inadequacy of diagnosis. In severe cases it may be very difficult to distinguish between infundibular obstruction of the right ventricular outflow tract from tight valvular stenosis. Dr. Lam has already mentioned his experience with the diagnostic error that resulted in a surgical fatality. The third reason, and perhaps the most important, is our experience with pulmonary valvulotomy alone. We have been more and more impressed by the significant gradient that results from pulmonary valvulotomy even when it is performed under direct vision. With total cardiac bypass it is our practice to complement valvulotomy by incision of the annulus and the distal outflow tract of the right ventricle itself. In this way the surgeon can assure himself that there is no obstructing moderator band or infundibular lesion proximal to the stenosed valve; even then relief of the gradient is not complete—at least at the immediate time of surgery. However, catheterization studies performed a year after operation are rewarded by the finding of normal anatomic and physiologic function.

Perhaps there is a basic difference in personality and nervous system that permits one surgeon to tolerate, and the other to resent, the unrelenting pressure of the ticking clock. I do not question that in the hands of a gifted technical surgeon like Dr. Lam, who enjoys this sort of operation, much can be accomplished in the short space of one minute. I do not question whether the operation can be done in this elapsed period of time, but I do raise the point as to whether it should be done. From the standpoint of surgical training it is my belief that this emphasis on speed constitutes some form of surgical pyrotechnics. I honestly believe that the emphasis on surgical speed is a step backward rather than forward.

It reminds me of that ancient story on the correct method of kissing an ostrich. Most of you will remember the graphic description of technique that is followed with the admonition, "but you've got to be quick!"

Much has taken place and has been discussed before this Society since the meeting in San Francisco a few years back. Perhaps it is well that four different approaches to the problem are still in use: the closed valvulotomy of Brock, the instantaneous valvulotomy of Lam, the cold valvulotomy of Swan, and the bypass valvulotomy of Effler. Perhaps time will be the deciding factor, but it must be remembered that this is a completely correctable disease and that our goal should be 100 per cent correction with a minimal mortality rate.

DR. JAMES ALASTAIR KEY, Toronto, Ontario.—I, too, would like to congratulate Dr. Lam on his presentation.

There is just one point which perhaps might be of some significance, and that is that I know Dr. Lam to be a keen musician, but I think he possibly doesn't like Puccini, because he seems to have an aversion to getting either his or his tiny patients' hands frozen!

However, it is quite possible, especially in dealing with children, that the use of an air-conditioned operating theater, and especially if one uses a volatile preparation for sterilization or cleansing of the skin, that Dr. Lam has been utilizing some degree of hypothermia of which he is not aware.

We certainly know in children that as much as a 2° drop in temperature can occur under these circumstances during the course of opening the chest and exposing the heart. Like other discussers, it would seem to me, therefore, that the results of Dr. Lam and Dr. Taber indeed bear witness to their surgical dexterity. Whether they justify the abandonment of hypothermia in the treatment of direct vision pulmonary valvotomy would seem more open to question.

DR. WILLIS J. POTTS, Chicago, Ill.—It is not a particularly pleasant thing to do but occasionally it is necessary: the consumption of fricasseed crow in public. The person who is going to observe this procedure with a certain amount of delight is Henry Swan.

For a number of years we employed the transventricular approach for the correction of pulmonary valvular stenosis. Approximately 100 children were operated upon by this technique with one operative death. The immediate results were excellent; in fact, spectacular. Since we had developed special valvulotomes and dilators for this procedure we continued to use the transventricular approach longer than we should have.

We now use the open direct visualization technique under hypothermia as described by Conrad Lam. We are not as fast as he, but usually complete operation on the fused valves in less than 3 minutes. We still use the transventricular approach for infants with huge hearts.

Because of recurrent stenosis of the valve we have had to re-operate on 7 children to date and undoubtedly will have to re-operate on more in the future. Although the children who required re-operation were tremendously improved for some years, all symptoms returned. At the second operation the valve cusps had so completely re-fused that it was impossible to see where the cusps had been separated.

During the past few years we have operated upon 42 children with isolated valvular stenosis under direct vision without mortality. Whether the cusps of the valve will again fuse, even though they have been completely opened, only time will tell.

For the surgical approach we prefer a Y-shaped incision and longitudinal splitting of the sternum. A Y-shaped incision is quite satisfactory, especially for boys. If there is any criticism of the appearance of the incision the boy can be sent to Yale and have his letter before matriculation.

PRESIDENT DE BAKEY.—I suppose, if it were really known, the path on the road to truth in science is strewn with the bones of fricasseed crow.

DR. BENSON B. ROE, San Francisco, Calif.—I think that Dr. Lam's excellent presentation and the paper before him of Dr. Mahoney are worthy of further support, with the return toward the simplified techniques which we all think are desirable for the reasons so well expounded.

However, in each of these series, and in the experience of all of us, there are these unavoidable errors in diagnosis, which confront us with an embarrassing problem in the operating room. I think, therefore, we should work further toward a compromise arrangement permitting us to continue using hypothermia, but having the pump-oxygenator available, without wasting this large amount of blood.

We will hear later, I hope, more about the Edglugate blood preservative developed by Drs. Smith, Brown, and Sealy. This method permits having the blood drawn and available where it can be quickly added to the pump-oxygenator and brought into use where these diagnostic errors arise. Blood drawn and anticoagulated in this manner can be kept for several days and used for other patients if not needed for the extracorporeal circuit.

DR. GEORGE H. A. CLOWES, JR., Cleveland, Ohio.—Since people are advocating either a very quick job at normal thermic levels (Dr. Lam) or the use of the oxygenator, taking all the time that is wanted (Dr. Effler), I would like to recommend the compromise.

In our clinic we have found it very convenient to follow the teaching of Ivan Brown and Converse Peirce on the matter of using hypothermia with an oxygenator. I draw this to your attention because one can use a smaller oxygenator, slower blood flows which require simple cannulations, and have a very easy time of it with no rush.

We have a series of patients that have been taken down to 25° C. With external cannulations of the femoral veins and the jugular vein in the neck, the type of catheters you can easily slide into these will permit quite adequate flows and maintain very satisfactory conditions at 25°, which may amount to only a quarter of the flow that is required at normal thermic conditions to maintain pH, adequate oxygenation, and CO_2 levels where they should be.

This we have tested thoroughly in dogs and have followed in the course of Peirce and Brown to go on to do it with patients. I recommend, for those who don't like to hurry, that this may be a very satisfactory way of getting around the problem and still saving the blood.

DR. TABER (Closing).—I would just like to emphasize two points that Dr. Lam mentioned in the paper. As is the case frequently in cardiovascular surgery, the operation is as good as the diagnosis. In our experience, valvular and infundibular stenosis are an extremely uncommon combination together, and the cardiolgists have been able to ferret out the cases of infundibular stenosis and not present those to us for a closed operation.

The diagnostic techniques have not been anything, I believe, that are unusual, consisting of angiocardiography, cinefluorography, and the usual catheterization studies.

The second and final comment would be with regard to the time for the valvotomy which has been mentioned by several discussers. I think if you were to use this technique you would find 1 to 1½ minutes an entirely adequate period. Multiple occlusion periods are, of course, possible if needed.

THE SURGICAL TREATMENT OF ISOLATED INFUNDIBULAR STENOSIS

Henry Swan, M.D., William P. Hederman, M.Ch. (by invitation), Philip S. Vigoda, M.D.** (by invitation), and S. Gilbert Blount, Jr., M.D. (by invitation), Denver, Colo.*

SOME difference of opinion exists concerning the relative frequency of subvalvular pulmonic stenosis with intact ventricular septum, or, as more commonly stated, isolated infundibular stenosis.

Paul Wood,[1] in a series of 750 cases of congenital heart disease, found that 2 per cent or 15 cases were isolated infundibular stenosis. Of all cases of pure pulmonic stenosis, he stated 4 out of 5 are valvular and 1 out of 5 is infundibular.[2] On the other hand, Campbell,[3] in his series of 1,130 cases of congenital heart disease of which 113 were pure pulmonic stenosis, has seen only 2 cases of isolated infundibular stenosis, only one of which was confirmed by surgery. Abbott[4] in her 1,000 autopsied cases of congenital heart disease reported only 2 cases of infundibular stenosis with closed interventricular septum.

From the first description of pure infundibular stenosis by Elliotson,[5] in 1830, until 1948, when general application of cardiac catheterization came into use, only 14 autopsied cases had been reported. Keith,[6] in his classic lectures on malformations of the heart, alludes to some cases of pure infundibular stenosis but the cases are not described adequately and we do not know whether any of his cases were previously reported.

Since that time, most reported series of pulmonic stenosis with intact interventricular septum have a few cases of what are believed to be pure infundibular stenosis. Besides the series of Wood and Campbell, already mentioned, Kjellberg[7] has reported 3 out of 25, Dow[8] 1 out of 8, Glover[9] 4 out of 25, Joos[10] 1 out of 26, Abrahams[11] 8 out of 69, Dimond[12] 2 out of 20, Kirklin[13, 14] 3 out of 19, and Van Loo and his co-workers[15] reported 6 cases of infundibular stenosis of which 4 were of the isolated variety. Brock,[16] in a more recent study, states that he has operated on 9 cases of infundibular stenosis as compared with

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Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

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Fig. 1.—Case 1 (M. Y.), white woman, aged 23. Preoperative electrocardiogram and x-ray. Cardiac catheter tracings showing preoperative gradient of 126 mm. Hg between pulmonary artery and right ventricle and postoperative gradient of 36 mm. Hg

111 cases of valvular stenosis. In a perusal of the literature since 1958,[17] about 60 cases of isolated infundibular stenosis have been reported. The great majority of these have been diagnosed at catheterization, a small number at operation, and the least number at autopsy.

We would like to report 5 cases of isolated infundibular stenosis treated surgically by outlining the operative treatment and the results.

CASE REPORTS

CASE 1.—M. Y., a 21-year-old white mother, was seen in 1953 with a 2½ year history of dyspnea on exertion and easy fatigability, but no other symptoms. A heart murmur had been detected at the age of 6 years and she had been restricted in activity by her parents. However, she had had an uneventful pregnancy 2 years before admission. She had had one episode of cyanosis in her youth after swimming a long distance.

Physical examination revealed a healthy girl with a Grade 4, rasping systolic murmur and a thrill, both maximal in the second and third left interspaces parasternally and definitely louder in the third space than in the first. The second pulmonic sound was diminished.

The *electrocardiogram* revealed right ventricular hypertrophy and right axis deviation. X-ray studies showed a heart size within normal limits with flattening in the main pulmonary artery area.

Cardiac catheterization showed a sharp fall in pressure from right ventricle to pulmonary artery, the former being 147 mm. Hg systolic and the latter 21 mm. Hg systolic. The actual level in the outflow tract at which this fall occurred was not noted exactly but was thought to be at the pulmonary valve. Oxygen saturation determinations showed no evidence of a left-to-right shunt.

In this first case, the preoperative diagnosis was isolated pulmonic valvular stenosis.

Operation: On Nov. 6, 1953, under general anesthesia, the patient was cooled to 30° C. A bilateral transverse thoracotomy incision was used and, when the pericardium was opened, it became obvious that there was a definite infundibular chamber in the outflow tract of the right ventricle which was beating out of phase with the rest of the ventricle. The chamber enlarged during early systole, then contracted during ventricular diastole. A definite line of demarcation between the main part of the ventricle and the chamber was clearly visible and the thrill commenced at that point. After inflow and outflow occlusion, the infundibular chamber was incised vertically through an area previously infiltrated with 1 per cent procaine. There was a stenotic ring at the lower end of the chamber with a 3.5 mm. aperture. The pulmonary valve was normal. Using a punch, the ring was excised in bites until a finger could easily be passed down into the right ventricle. The incision in the infundibulum was closed with interrupted mattress sutures of silk. Total occlusion of circulation lasted 5 minutes and 10 seconds. After this, the thrill was markedly diminished and the infundibulum now beat in phase with the ventricle.

The *postoperative course* was uneventful, and when seen in July, 1954, she was asymptomatic. A murmur was still present but the second pulmonic sound was now normal. An electrocardiogram revealed considerable regression of the right ventricular hypertrophy. Cardiac catheterization 8 months after operation showed a pulmonary artery pressure of 27/6 mm. Hg. On withdrawal of the catheter an area of pressure of 29/0 was found and on withdrawing further into the right ventricle a jump to 66 mm. Hg systolic occurred (as compared with a preoperative pressure of 147 mm. Hg). No further studies have been performed to see if there has been any further change in ventricular pressure in the last 5 years (see Fig. 1).

CASE 2.—L. H., a 9-year-old white boy, had a known heart murmur since 1½ years of age. At that time he had had attacks of fainting accompanied by cyanosis of the face and rigidity of the whole body. These attacks ceased at the age of 5. He had some dyspnea on

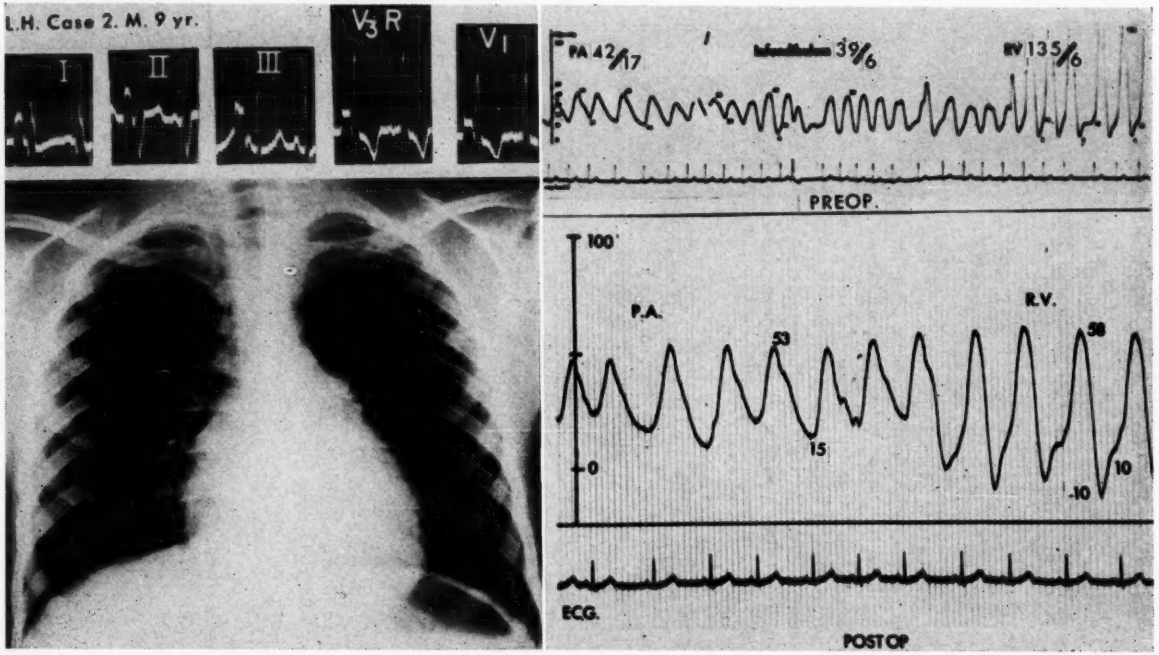

Fig. 2.—Case 2 (L. H.), 9-year-old white boy. Catheterization studies showing a typical infundibular pressure chamber and an over-all systolic gradient of 93 mm. Hg preoperatively and no gradient postoperatively.

exertion and fatigability, but no squatting or cyanosis other than that mentioned. He was admitted to Colorado General Hospital because of a skull fracture on Dec. 3, 1955, and later referred to the Cardiology Department.

Physical examination revealed an undersized, chronically ill child. A slight right ventricular lift was felt along the lower left sternal border. A marked systolic thrill maximal in the second left intercostal space was palpated close to the sternum. Auscultation revealed a harsh, Grade 4 systolic murmur in the second left intercostal space which radiated to the apex and became more high pitched as one moved downward.

The *electrocardiogram* revealed right ventricular hypertrophy.

Fluoroscopy showed decreased lung vascularity with a normal aorta and a prominent main pulmonary artery. The right atrium and right ventricle were enlarged.

Cardiac catheterization, on Jan. 20, 1956, showed that the right ventricular pressure was markedly elevated at rest, 135/6 mm. Hg. The pressure in the infundibulum was only 39/6, and the pulmonary artery pressure was 40/17. The infundibular chamber appeared to extend from low in the right ventricle to the pulmonary valve. Peripheral arterial saturation was 97.3 per cent at rest and 89.8 per cent at exercise. No evidence of left-to-right shunt was shown by the O_2 saturation studies.

The preoperative diagnosis was isolated infundibular valvular stenosis, possibly with a right-to-left shunt on exercise through a patent foramen ovale.

Operation: On Jan. 24, 1956, under general anesthesia, the patient was cooled to 26.5° C. The pulmonary artery was of normal size. An obvious infundibular chamber was seen which beat out of time with the rest of the right ventricle. The vigorous thrill commenced over the infundibular chamber which was 3 mm. thick. The tight fibrous infundibular stenosis, about 3 to 4 mm. in diameter, was treated by excising a portion of crista supraventricularis, the ring of fibrous tissue, and some muscle. A finger was then passed into the main cavity of the right ventricle and no ventricular septal defect could be felt. No red blood appeared in the right ventricle during the procedure indicating that both septa were intact. A running mattress suture closed the incision during release of inferior vena caval occlusion. Total occlusion time was 5 minutes and 40 seconds. Palpation revealed no thrill remaining over the infundibulum. The patient made an uneventful recovery.

Postoperative cardiac catheterization on Feb. 15, 1956, showed that no systolic pressure gradient remained between right ventricle and pulmonary artery, the systolic pressure in each being 55 mm. Hg. The O_2 saturation studies revealed no evidence of left-to-right shunt. The arterial blood was fully saturated with oxygen at rest and after exercise.

Follow-up observation in June, 1957, 1½ years after operation, showed the patient to be asymptomatic with no exercise intolerance. The electrocardiogram still showed some right ventricular outflow tract hypertrophy but a definite improvement had occurred. A Grade 3 murmur still remained, but the second pulmonic sound was increased. The patient no longer had pulmonic stenosis but had mild pulmonary hypertension (see Fig. 2).

CASE 3.—J. W., a 21-year-old white woman, had a known heart murmur since birth, but had had no symptoms until 6 months prior to admission when she developed chills and fever and subsequently complained of easy fatigability and a considerably reduced exercise tolerance. She had had two fainting spells.

Physical examination, when she was first seen in December, 1956, revealed a marked systolic thrill and a harsh, rasping Grade 6 systolic murmur over the entire precordium, both maximal close to the sternum in the third left intercostal space. The murmur was very loud and could be heard at some distance from the chest wall. It was louder in the third than in the first intercostal space, and as loud in the fourth as in the second. A sustained thrust was felt at the lower left sternal border.

The *electrocardiogram* revealed sinus tachycardia, 138 per minute, and right ventricular hypertrophy.

Fluoroscopy showed an enlarged pulmonary trunk with normal left and right pulmonary arteries. The right side of the heart was enlarged.

Fig. 3.—Case 3 (J. W.), 21-year-old white woman. Preoperative studies show systolic gradient of 77 mm. Hg and, in addition, a Venturi effect while postoperative pressures show no systolic gradient.

Cardiac catheterization, on Dec. 7, 1956, showed that the pressure in the pulmonary artery was 13/8 mm. Hg and that an abrupt rise to 90/8 mm. Hg occurred at some distance below the pulmonary valve in the infundibular region of the right ventricle. There was no pressure change at the pulmonary valve, itself. No evidence of a shunt or peripheral arterial O_2 desaturation was found.

The preoperative diagnosis was isolated infundibular pulmonic stenosis.

Operation: On Dec. 11, 1956, with the patient under general anesthesia and hypothermia, a bilateral transverse thoracotomy was used. The lungs were very pale. The heart was slightly enlarged. A clear-cut infundibular chamber was seen distal to a line of demarcation, 4 cm. below the pulmonary valve. The systolic thrill was maximal in the chamber and diminished along the pulmonary artery which showed only slight post-stenotic dilatation.

The wall of the infundibulum was incised after inflow-outflow occlusion and neostigmine bradycardia. A moderate-sized chamber was entered. The stenosis at the lower end admitted the tip of the index finger and was composed of a dense fibrous ring and, in addition, comprising its posterior border, was a broad band of muscle running obliquely upward across the lumen of the ventricle. Using scissors and forceps, the entire ring and portions of the muscle were excised until it was possible to admit three fingers through the opening. The absence of red blood in the right ventricle eliminated the possibility of a ventricular septal defect. The wall of the infundibulum was 3 mm. thick, while the wall of the right ventricle was 11 mm. thick. The incision was closed with interrupted sutures. Occlusion time was 5 minutes and 5 seconds. Recovery was uneventful.

Postoperative catheterization, on July 23, 1957, showed that the systolic pressure in both the right ventricle and the pulmonary artery was 26 mm. Hg, there being no gradient whatsoever. There was still no evidence of a shunt and peripheral arterial saturation was again normal. Indicator dilution studies were normal.

The *electrocardiogram* showed only slight residual right ventricular hypertrophy. When last seen, 8 months after operation, the patient was asymptomatic. The thrill had disappeared, but a Grade 2 systolic murmur in the second left interspace remained. It was concluded that the patient was cured (see Fig. 3).

CASE 4.—D. S., a 20-year-old white man, was first seen in May, 1954. He had been blue for 3 days after birth. A heart murmur was noted. Growth was normal. After the age of 10, he began to have syncopal attacks about every 6 months up to the age of 15, and more recently he had experienced mild exercise intolerance. He was said to have had a dusky complexion, but no definite proof of cyanosis had been established.

Physical examination of this well-developed young man revealed slight duskiness of nail beds and lips, but no definite central cyanosis. Prominent "a" waves were noted in the neck. A slight right ventricular lift was present at lower left sternal border. A systolic thrill and a harsh, Grade 4 systolic murmur were present over the precordium, maximal over the inner end of the second and third left intercostal spaces.

The *electrocardiogram* suggested right ventricular hypertrophy.

Fluoroscopy revealed enlargement of the right atrium and the right ventricle. Prominent left but normal right and main pulmonary arteries were noted.

Cardiac catheterization, on July 20, 1954, showed a gradient in systolic pressures of 75 mm. Hg between main pulmonary artery and right ventricle; right ventricle, 100/-3 mm. Hg and pulmonary artery, 19/6. However, this rise seemed to occur about one third of the way down the left border of the heart and not at the pulmonary valve level. There was no evidence of a shunt and the systemic arterial O_2 saturation was normal. The preoperative diagnosis was isolated infundibular pulmonic stenosis.

Operation: On April 2, 1957, under general anesthesia, the patient was cooled to 30.5° C. Bilateral thoracotomy, using the fourth intercostal space on the right and the third on the left side, was performed. The heart was large, mainly on the right side, and the right ventricle was hypertrophied. A very small infundibular chamber, about 1 cm. long, with a

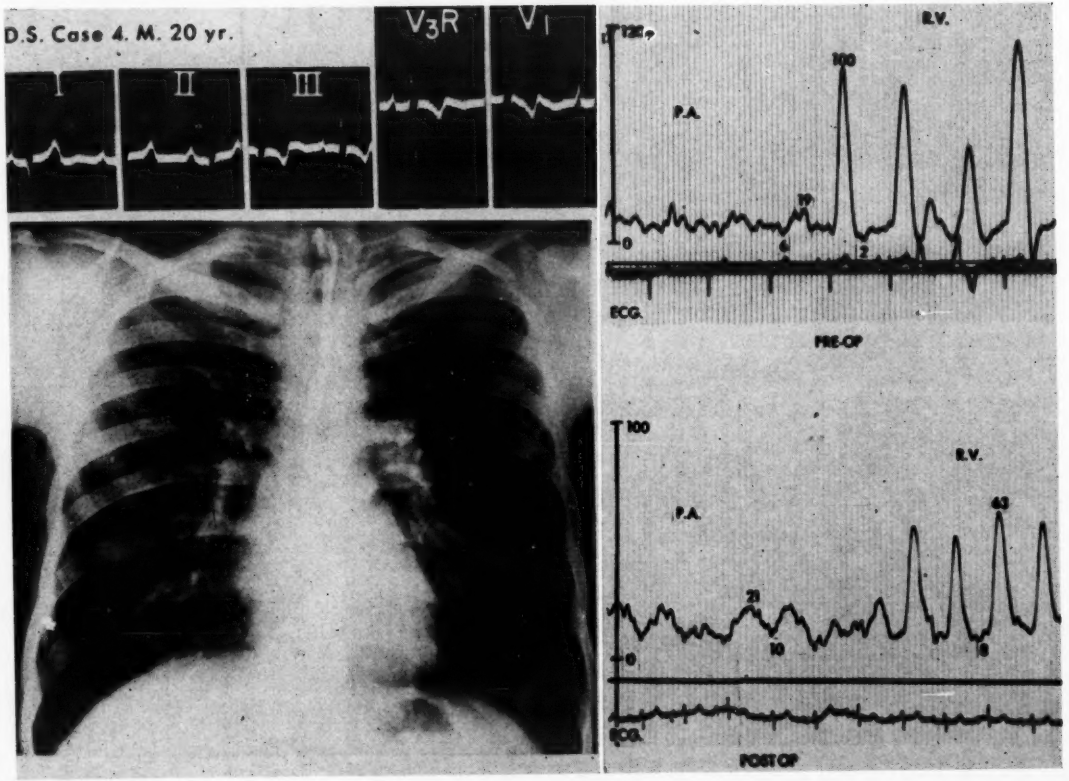

Fig. 4.—Case 4 (D. S.), 20-year-old white man. Preoperative gradient of 81 mm. Hg and postoperative gradient of 62 mm. Hg.

thin wall, was seen. The systolic thrill began in this chamber and was propagated on to the pulmonary artery where it was maximal over the mild post-stenotic dilatation. The outflow tract was infiltrated with 1 per cent procaine and, using inflow-outflow occlusion and neostigmine bradycardia, an incision was made in the right ventricle extending up the outflow tract and into the small infundibular chamber. This involved cutting through a fibrous stenotic ring. It was found that the infundibular chamber was triangular in section as the obstructing diaphragm ran upward and backward and almost fused with the pulmonary valve posteriorly. As much as possible of the obstructing sheet was excised. Palpation upward revealed a normal pulmonary valve and palpation downward revealed firm muscle around the finger in the outflow tract, but no actual stenosis. Closure was effected by a running suture in the incision. Total occlusion time was 4½ minutes. Recovery was uneventful.

Postoperative catheterization, on May 16, 1957, 6 weeks after operation, showed a pressure of 63/8 in the right ventricle and a pressure of 21/10 in the pulmonary artery, and a systolic gradient of 42 mm. Hg compared with 81 mm. Hg before operation. An indicator dilution curve revealed no evidence of a right-to-left shunt.

The *electrocardiogram* remained unchanged.

Since operation he has had an increased exercise tolerance and has felt well. There remains a Grade 2 systolic murmur of diminished intensity. The patient is clearly improved (see Fig. 4).

CASE 5.—L. D., a 9½-year-old white girl, was admitted in August, 1958. She had been known to have a heart murmur for 4 years prior to admission and had been having mild dyspnea on exertion and some fatigability. The previous winter she had had a severe upper respiratory tract infection.

Physical examination revealed a right ventricular lift along the lower left sternal border. A thrill and a harsh, Grade 4 systolic murmur were noted over the precordium, maximal in the second left intercostal space, but louder in the third than in the first space.

The *electrocardiogram* showed right ventricular hypertrophy.

Fluoroscopy revealed slight prominence of the main pulmonary artery and an enlarged right atrium and right ventricle.

Cardiac catheterization, on Aug. 15, 1958, showed a pulmonary artery pressure of 24/11 and a right ventricular pressure of 99/0 mm. Hg. The rise in pressure occurred low in the right ventricle. There was no evidence of a shunt in either direction.

The preoperative diagnosis was isolated infundibular pulmonic stenosis.

Operation: On Oct. 27, 1958, under ether anesthesia, the patient was cooled to 30.5° C. A large infundibular chamber with a thin wall was found while the main right ventricular wall was thick. The pulmonary artery was normal in size. The thrill commenced at the lower border of the infundibular chamber.

On opening the chamber, it was found that the stenosis was formed by a muscular diaphragm with two small fibrous-rimmed holes in it. The pulmonary valve was normal. The stenosis was excised by extensive dissection with knife and scissors. After this procedure, the chordae tendineae of the tricuspid valve were easily seen. No red blood entered the right ventricle. The incision was closed by tying previously placed stay sutures. Total occlusion time was 4 minutes, 50 seconds. The thrill had now disappeared and the pulmonary artery was pulsating well.

Postoperative catheterization, on March 20, 1959, showed that the pressure in the infundibular chamber was 20/0 mm. Hg and in the body of the right ventricle 30/0 mm. Hg; thus, the systolic pressure gradient had fallen to 10 mm. Hg (75 mm. Hg before operation) (see Fig. 5).

PATHOLOGY

It appears that infundibular stenosis is caused by arrest of the normal involution of the bulbus cordis which should be incorporated into the right

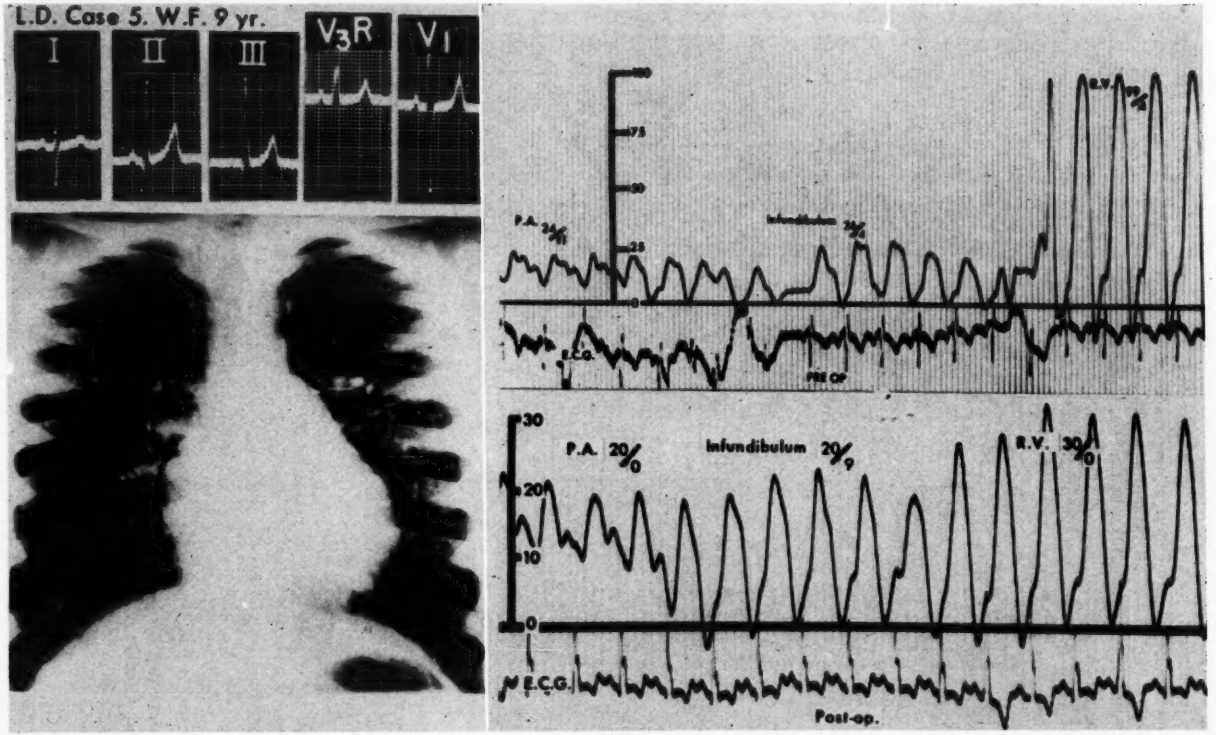

Fig. 5.—Case 5 (L. D.), 9-year-old white girl. Preoperative catheterization showing systolic pressure gradient of 75 mm. Hg and an infundibular pressure chamber. Postoperative catheterization showing a gradient of 10 mm. Hg and an infundibular pressure chamber still present.

ventricle by the end of the second month of intrauterine life, thus forming the outflow tract of the right ventricle.[6]

The stenosis, it is said, may be of two types: (1) fibrous and muscular tissue create a narrowed area in some portion of the infundibulum dividing the right ventricle into two chambers of unequal size, the one with an hypertrophied wall, the other dilated and thin walled; and (2) the infundibulum is shrunken in size with thick muscular walls constituting a fusiform stenotic outlet extending over some distance.[18] In our series, we have not encountered this latter type.

CLINICAL DIAGNOSIS

History.—A heart murmur may have been first noted at any age. Such a murmur, of course, has really been present since birth. The symptoms, if any, are identical with those of valvular pulmonic stenosis and include exertional dyspnea, fatigue, syncope, dizziness, anginal pain and, eventually, edema and right heart failure. Clubbing and central cyanosis indicates the presence of a septal defect in both groups and rules out an isolated obstruction. The history is of no aid in delineating the site of the stenosis.

Physical Findings.—The following points may help to differentiate infundibular stenosis from valvular stenosis: (1) right ventricular precordial lift may be absent in very low infundibular stenosis, (2) the thrill and systolic murmur are usually maximal in the third left intercostal space in infundibular stenosis and higher up in valvular stenosis,[19] (3) the second heart sound may be widely split in infundibular stenosis with a normal or diminished pulmonary component, (4) usually no post-stenotic dilatation of the pulmonary artery is seen on x-ray in infundibular stenosis and, in the right anterior oblique view, the left lower mid-segment may bulge, and (5) on fluoroscopy, the pulsations of the main pulmonary artery are increased in valvular stenosis, but not in the infundibular type.

Looking at our cases, the only one of the above features which occurred constantly was the lower site of the murmur and thrill. These were always louder in the third than in the first space.

Electrocardiogram.—Right ventricular hypertrophy is present in both types of obstruction.

Fluoroscopy.—One would expect to note less post-stenotic dilatation of the pulmonary artery with infundibular stenosis but, in our cases, we were unable to correlate the fluoroscopic findings with the actual anatomy seen at surgery in 2 of the 5 cases. When the extremes (either very pronounced dilatation or apparent diminution in pulmonary artery size) are present, the finding is probably helpful; but in the intermediate stages, the fluoroscopy observations do not aid in the differential diagnosis.

Thus, if our patients are representative, we find no important advance has been made in the clinical differentiation between isolated valvular and infundibular stenosis since Barie,[19] in 1895, noted that the murmur and thrill were located lower on the precordium in infundibular stenosis.

Cardiac Catheterization.—It has been assumed that cardiac catheterization would be efficient in revealing three distinct pressure zones in pulling back from pulmonary artery to right ventricle, the lowest mean pressure being in the infundibulum.[11] In going from pulmonary artery through the valve into the infundibulum, the systolic pressure rises abruptly while the diastolic pressure remains constant. Moreover, the right ventricular pressure curve does not appear until the catheter tip is well below the valve level.

Despite this thesis, at times the diagnosis of infundibular stenosis comes as a surprise to the surgeon and the cardiologist at operation. Fabricius,[21] reporting on 50 patients submitted to pulmonary valvulotomy for either isolated pulmonary stenosis or the tetralogy of Fallot, had 5 cases in which catheterization was interpreted as revealing a valvular-type of stenosis yet, at operation, infundibular stenosis was present. Antonius,[22] in reporting 39 cases akin to those of Fabricius, found 11 cases of infundibular stenosis at operation of which only 2 were diagnosed by catheterization. This discrepancy has been commented upon by almost all groups with extensive experience in the surgery of pulmonic stenosis.

Kirklin[13] has stated that a sudden transition from pulmonary artery to ventricular pressure curve can occur not only in valvular stenosis but also in pure infundibular stenosis, if the obstruction is situated close to the valve. Certainly, this has been our own experience.

In 4 of our cases, the right ventricular pressure curve did not appear until the catheter was well below the usual site of the pulmonary valve. In the one exception, the site was not noted. We found this observation, when present, to be uniformly valid and we think that this is probably the best contribution of cardiac catheterization toward confirming the diagnosis of infundibular stenosis.

Other Methods of Diagnosis.—Rudhe[7, 23] and the group at the Karolinska Institute in Sweden describe selective angiocardiography and electrokymography as giving excellent results in differentiating valvular from infundibular stenosis. We have had no experience with these techniques.

Differential Diagnosis.—Besides valvular stenosis, the most difficult disease to differentiate from mild infundibular stenosis is the maladie de Roger. In mild infundibular stenosis the split of the second sound is wide and the thrill and murmur may be situated higher than in maladie de Roger. As the severity of the lesion increases, this differential diagnosis becomes much easier.[2]

Other entities that may simulate mild infundibular stenosis are atrial septal defect and mild aortic or subaortic stenosis. Careful clinical evaluation will avoid confusion with these entities. The differentiation between severe infundibular stenosis with patent foramen ovale and the tetralogy of Fallot, while very important, is not pertinent to this discussion of pulmonic stenosis with intact septa.

SURGICAL THERAPY

Like pulmonary valvular stenosis, the actual manipulative period of the excision of infundibular stenosis does not need to be very long, perhaps 4 to 6

minutes. Therefore, the technique of hypothermia has proved quite safe and satisfactory for this procedure. There appears to have been a widespread opinion that incision into the human ventricle is apt to precipitate ventricular fibrillation in the hypothermic patient. This opinion was, no doubt, derived from animal experimentation, since, at 25° C., right ventricular incision in dogs invariably precipitates fibrillation. This transference between species is merely another example of the danger of translating canine cardiac responses to man. We have incised and later sutured the hypothermic right ventricular myocardium, after infiltration with 1 per cent procaine, in 16 patients whose rectal temperatures were between 26 and 31° C. and have not seen a single episode of ventricular fibrillation as a result of this incision. As in other operations suitable for hypothermia, accurate preoperative diagnosis relative to the integrity of the cardiac septa is important, lest the surgeon find himself at the operating table staring at an unexpected malformation, the correction of which would require cardiopulmonary bypass. It is not critical, however, to distinguish infundibular from valvular stenosis since both are readily and safely treated using hypothermia alone.

The transverse sternal splitting incision, utilizing the fourth interspace on the right and the third on the left, has proved ideal for both the vena cava dissections and the infundibular procedure. A vertical sternal splitting procedure may be equally effective, provided that the skin incision is transverse and submammary to avoid the disfiguring scar usually left when the vertical sternal splitting incision is employed.

Positioning of the patient so that the cardiotomy is as superior as possible is important to avoid trapping air, as it is in all other operations on the heart.

After wide pericardiotomy to expose the myocardium, inspection of the right ventricle has immediately revealed the site of the pulmonic obstruction in all of our cases. An infundibular chamber, whether small or large, has been seen, separated from the remainder of the hypertrophied tense ventricle by a distinct groove crossing the outflow tract. The chamber bulges during early systole, thus having a paradoxical motion which puts it out of phase with the rest of the ventricle. (One would suppose that this motion might be visible on occasion at the preoperative fluoroscopy.) The vigorous systolic thrill invariably begins in the infundibular chamber, although in 1 patient with a very high obstruction (Case 4, D. S.), the thrill did not become maximal until the palpating finger was moved about 1 inch beyond the valve ring. The pulmonary artery in this patient also showed slightly more post-stenotic dilatation than was seen in the other patients, although in none of them did this enlargement of the pulmonary artery approach that commonly seen with valvular disease.

Tapes are placed around the two venae cavae near their entrance into the auricle. We have routinely infiltrated the myocardium of the outflow tract above and below the infundibular groove with 1 per cent procaine to diminish the number of stimuli aroused by incision, retraction, and suturing of myocardium. This step may not be necessary but, since no episodes of ventricular fibrillation have occurred, we have continued its use. Stay sutures are placed to each side of the proposed incision, and one at each end, to aid in the rapid closure, which can be done while circulation is being restored.

When all is ready, inflow occlusion is performed by traction on the tapes around the venae cavae. The aorta is cross-clamped about 1 inch above the heart and 1.0 to 1.5 ml. of 1:4,000 neostigmine is perfused into the coronary circulation by injection into the root of the aorta. The aortic clamp is then removed, and both aorta and pulmonary artery are clamped as close to the aortic roots as possible. This clamp is designed to stop coronary blood flow and to prevent back bleeding from pulmonary artery. The incision into the ventricle must then be made very rapidly so that distention of that structure will not occur.

The incision begins in the infundibular chamber when this structure is sufficiently large. It may traverse the stenosis or extend to a point just above it, as the occasion demands. Through this incision, the obstructing tissue is widely resected using whatever instruments the operator selects. Punches, scissors, and the knife may all be needed for a given situation. The extent of the resection should be as wide as is compatible with safety. The interventricular septum and the wall of the ventricle are, of course, preserved, but muscular bands involving the crista supraventricularis may be resected.

The failure of bright red blood to enter the right ventricle is taken as proof that no septal defect, however small, is present.

On conclusion of the definitive portion of the infundibular resection, the assistant pulls up on the stay sutures and the closure of the ventriculotomy by continuous suture is begun. At this point, blood is allowed to enter the right atrium and air is expelled from the heart via the incision. The clamp is then removed from the aorta and pulmonary artery so that blood flow to lungs and body is resumed. There may be some leakage of blood from the ventriculotomy during this period, but this is minimized by the assistant as the operator rapidly places the first layer of the continuous suture, thus sealing the incision. A second layer creating the so-called "baseball stitch" may now be placed leisurely, and reinforced with interrupted sutures as seems indicated. We have frequently reinforced this closure with a patch of pericardium sewn to the myocardium.

After the circulation seems satisfactory, the pericardium may be loosely closed, chest tubes placed, and the incision closed in the manner of the surgeon's choice.

RESULTS

Of the 5 patients, 2 had mild residual gradients, 1 had no gradient but a mild pulmonary hypertension (50 mm. Hg), while the other 2 had normal hemodynamics. All patients were much improved clinically, and it is felt that they now have cardiovascular physiology compatible with full exercise and long life.

SUMMARY

1. Of the 5 cases of isolated infundibular pulmonic stenosis presented, there was a correct diagnosis preoperatively in 4. The diagnostic criteria are discussed.

2. Operation was performed in each case during hypothermia, resecting the obstructing tissue under direct vision via a ventriculotomy.

3. Hypothermia is ideally suited for the surgical treatment of isolated infundibular stenosis, since either valvular or infundibular obstruction can be effectively and safely treated using this technique alone.

ADDENDUM

Since this report was made, 3 additional patients have been operated upon by the same method with excellent results.

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Discussion

DR. JOHANN L. EHRENHAFT, Iowa City, Iowa.—All of us who are doing open intracardiac surgery have and will encounter this relatively rare congenital anomaly under discussion. We have seen it in 5 patients. Being advocates of both methods, hypothermia and extracorporeal circulation, we have used the extracorporeal circuit in patients with infundibular muscular stenosis by preference, even though we prefer hypothermia for correction of pure valvular pulmonic stenosis. As it has been stated, the differential diagnosis between a valvular pulmonic stenosis and an infundibular muscular stenosis without an associated septal defect can at times be difficult. This is especially true if the muscular infundibular stenosis is located distal in the right ventricular outflow tract. The time required to completely resect this often massive muscular ridge is sometimes longer than one can gain by the use of hypothermia alone. This was brought home to us by a patient in whom we resected about 15 grams of right ventricular muscle before the right ventricular outflow tract obstruction was completely relieved and this required about 40 minutes.

If the infundibular muscular mass is completely resected, no residual thrill or murmur should exist and there should be no pressure differential between the right ventricle, the right ventricular outflow tract, and the pulmonary artery.

DR. GILBERT S. CAMPBELL, Oklahoma City, Okla.—A patient with isolated infundibular obstruction with an interesting antecedent history was recently admitted to the University of Oklahoma Hospital.

(Slide) I think the anatomy is depicted fairly well in this drawing by Dr. Richardson.

This next slide will show what was seen at the time of cardiotomy into the infundibular chamber.

This next slide will show a blow-up of the infundibular diaphragm.

This patient had a Brock procedure done in June of 1956, and the knife had been introduced and manipulated only in the infundibular chamber and the pulmonary artery. On re-admission in late March of this year the right ventricular systolic pressure was 164 mm. Hg. Following excision of this infundibular diaphragm, the systolic pressure in the right ventricle was 45 mm. Hg.

To date we have operated upon 11 patients at Oklahoma, and the defects include tetralogy of Fallot, partial A-V canal, atrial septal defect, infundibular stenosis (shown here), and isolated pulmonic stenosis. The mortality has been zero per cent.

DR. PAUL W. SANGER, Charlotte, N. C.—I would like to congratulate Dr. Hederman on his excellent English and his well-organized paper.

There is one thing I did not understand which I would like for him to explain. I thought he made the statement that with infundibular stenosis he also got post-stenotic dilatation, as we always get in valvular stenosis. This is a finding which has never been reported before and is against all hemodynamic principles as applied to post-stenotic dilatation. It has been an accepted diagnostic differentiating point that when post-stenotic dilatation occurred in the pulomary artery it was unquestionably always due to a valvular stenosis.

DR. FRANK GERBODE, San Francisco, Calif.—My ballot certainly is in favor of using extracorporeal circulation with most operations for relief of pulmonic stenosis, reserving hypothermia for the very young patients with valvular stenosis.

We have seen congenital infundibular stenosis in patients who have been very carefully screened and were thought to have pure valvular stenosis, and we have also found that there are not infrequently small interventricular defects associated with high infundibular stenoses.

Although it is possible, as has been shown by Henry Swan's very nice work, to resect the infundibulum utilizing hypothermia, my own belief is that extracorporeal circulation gives more security and the opportunity to perform a more complete operation.

In regard to Conrad Lam's paper, I am reminded of work we did in the experimental laboratory some years ago, when we, too, were studying hypothermia and pulmonic valve insufficiency. We wanted to resect the entire pulmonary valve. I developed a very nice technique using hypothermia; then one day I came into the laboratory and found most of the dogs had already been done by one of the young men without the aid of hypothermia and with a lower mortality rate than when hypothermia was used. This merely shows that one can usually do an open cutting procedure on the pulmonic valve without metabolic or circulatory support, but I certainly agree with Don Effler and some of the others that rapidity in this sort of thing is not always desirable. Accuracy and the possibility of having to extend the operation make the use of extracorporeal circulation most desirable. At the present time I do not believe that there is much inherent danger in using a properly designed and operated pump-oxygenator system.

DR. HENRY SWAN, II, Denver, Colo.—I would like to respond to Dr. Gerbode by saying that we don't feel in any way that we are casting a vote at this time for any type of technique. We use hypothermia; we use cardiopulmonary bypass. We have happened to use a combination of both rather frequently. We tend to use in our clinic the one which in our hands gives the best results to the patient at the lowest risk.

The only real argument we have for using the open valvuloplasty and resection of the infundibulum using hypothermia is the very satisfactory end results achieved, Dr. Gerbode, as objectively measured in the vast majority of these patients, and the fact that in some 65 such patients there has not been a death. So we feel that this particular technique and this particular argument is pertinent to the use of the method.

DR. HEDERMAN (Closing).—First, I would like to thank the discussers for their suggestions.

Two questions in particular I would like to reply to, one of Dr. Sanger, who commented on the post-stenotic dilatation. There was 1 patient who had very definite post-stenotic dilatation, and this case was a boy who had an extremely high obstruction. He had a very, very small triangular infundibular chamber, right up against the pulmonary valve, and the actual septum ran obliquely, so that posteriorly the septum was right up against the valve, and anteriorly there was only 1 cm. distance between the valve ring and the lower edge of the infundibular chamber.

It is easy to see that in this instance the jet of blood coming through the infundibular stenosis, which was very tight in this case, would go right through the pulmonary valve and create the post-stenotic dilatation in any of the ways that have been ascribed to be the cause of this condition.

I think this case also emphasizes our statement that it is not always possible to diagnose this condition preoperatively. Very careful cardiac catheterization will be needed in such cases as this, to differentiate either the infundibular chamber or the fact that the stenosis occurred a little below the valve. It is interesting that this boy did show the lower site of murmur and thrill, which was described so many years ago by Barrie, and none of our more modern methods were effective. So we feel that this is one of the reasons for doing these cases of pulmonary valvular stenosis under hypothermia rather than under normothermia, because it is possible, even with careful catheterization, to run into this kind of diagnostic difficulty with a very high infundibular stenosis. I think Kirklin has also commented on this in a paper some years ago.

Now the second question, if I am not running over my time. Dr. Gerbode mentioned the I. V. effect. I should have added that in all our cases no red blood came into the right ventricle during the procedure.

Finally, Dr. De Bakey, I would like to thank the Association and members for this privilege of speaking on this side of the Atlantic to you all.

SURGICAL EXPERIENCES IN THE TREATMENT OF CONGENITAL MITRAL STENOSIS AND MITRAL INSUFFICIENCY

George W. B. Starkey, M.D., Boston, Mass.

CONGENITAL mitral valvular lesions are rare cardiac anomalies but can cause severe incapacitation and death in children. It would appear that some of these lesions are amenable to surgical therapy. At the Boston Children's Medical Center, 5 patients with severe congenital mitral stenosis and 2 with congenital mitral insufficiency have been operated upon between 1955 and 1958. The clinical, pathologic, surgical, and hemodynamic aspects of these cases will be discussed.

CONGENITAL MITRAL STENOSIS

Eleven cases of "pure" or uncomplicated congenital mitral stenosis were found in the literature. There were 38 additional cases but these were associated with other cardiovascular anomalies, usually left sided, such as, aortic stenosis, coarctation, patent ductus arteriosus, etc. Thirty-four of these cases were reviewed by Ferencz[1] and his associates and 9 new cases were added. Bower,[2] Maxwell and Young,[3] Kjellberg,[4] Braudo,[5] and Bernstein[6] and their co-workers have reported 7 further cases.

The prognosis in congenital mitral stenosis uncomplicated by other valvular or aortic lesions is poor, as pointed out by Braudo, since 8 of the 10 patients he reviewed were dead under the age of 2 years. Of the 5 in the literature who were operated upon only 2 were alive at the time they were reported, 1 for at least 7 months and another for 16 months.

Clinical Material.—

There were 5 patients with congenital mitral stenosis operated upon at the Boston Children's Medical Center. The age range was 2½ to 15 years. There were 3 girls and 2 boys. The diagnosis was made on the basis of the early age of detection of a mitral diastolic murmur (between the ages of 2 weeks and 14 months in 4 and at 5 years in the fifth patient). There was no history or other evidence of rheumatic fever.

All these children were very ill and in congestive failure. Severe respiratory infections, underdevelopment, and dyspnea were present in all. Three of

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This work was aided by grants from the Massachusetts Heart Association.

Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

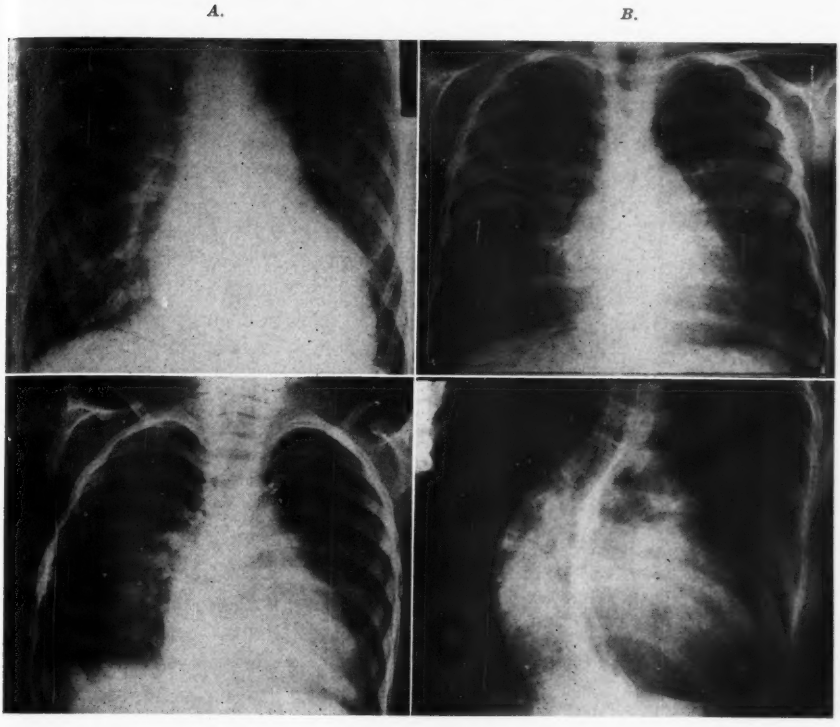

Fig. 1.—Congenital mitral stenosis. Preoperative roentgenograms. *A*, Case 1; *B*, Case 2; *C*, Case 3; *D*, Case 4; and *E*, Case 5.

the 5 patients had had repeated bouts of syncope, often accompanied by cyanosis. A fourth patient had grand mal seizures accompanied by cyanosis during bouts of crying. Hepatomegaly was noted in all 5 patients, splenomegaly in 3. The cardiac findings revealed normal sinus rhythm, an apical diastolic rumbling murmur, loud P_2, P pulmonale in all 5 patients. An apical systolic blowing murmur was found in 3 and right ventricular hypertrophy in 4. By x-ray examination there was cardiomegaly in all, with enlargement of the right ventricle, left atrium, and pulmonary artery (Fig. 1).

Four patients were catheterized preoperatively. There was evidence of marked elevation in pulmonary capillary pressure (27 to 30 mm. Hg mean), reflecting obstruction at the left atrial level. There was also increased pulmonary vascular resistance from 4.0 to 10 units (normal 3 units). In 2 patients studied postoperatively, 1 showed reduction in pulmonary artery pressure and both showed reduction in pulmonary capillary pressures.

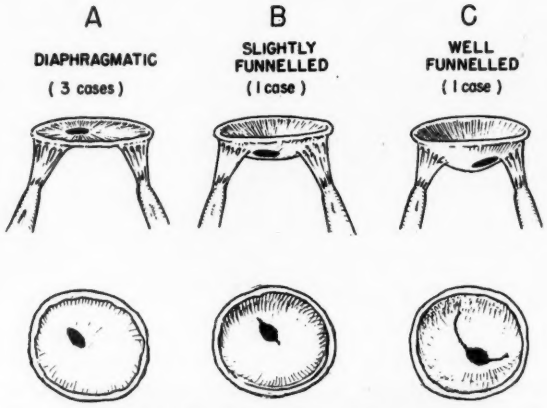

Fig. 2.—Congenital mitral stenosis. Schematic representation of valve types encountered at the time of surgery.

Surgical and Pathologic Considerations.—

Four of these patients were operated upon by the "closed" method using a standard left fourth intercostal space incision. There was one death on the fifth postoperative day for reasons that were not clear. Actually this patient had been doing quite well but died very suddenly after a meal, accompanied possibly by aspiration of food. No postmortem was obtained. A fifth patient was operated upon by the "open" method using a pump-oxygenator. At the end of the procedure the heart began to fail and could not be resuscitated.

All five patients had very large left atria. The junction of the appendage with the left atrium was small in most of these children, allowing entry only of the operator's fifth finger. There was no evidence of cor triatriatum. This was established by feeling both the mitral valve and at least one pulmonary vein orifice communicating with the single left atrial chamber approached by

the appendage. Three of the valves were quite flat, thickened, and diaphragmatic with either no or poorly defined commissures (Fig. 2). All three of these required incision with a guillotine knife. The fourth valve was well funnelled and had quite well-defined commissures. This valve was opened with the finger alone. The fifth patient operated upon with the aid of the pump-oxygenator had a funnelled valve, but thickened leaflets with practically no commissural definition. This valve also required incision. In all cases there was shortening

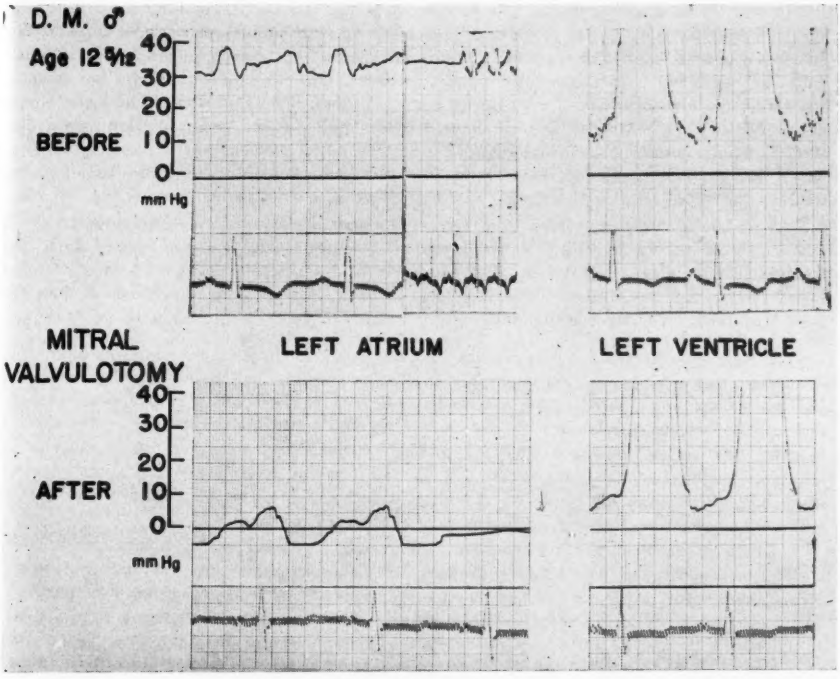

Fig. 3.—Congenital mitral stenosis (Case 1, D. M.). Direct readings at operation showed a left atrial—left ventricular gradient of 23 mm. Hg. There was no gradient post-commissurotomy.

and some fusion of the chordae tendineae. The atrial appendages all showed endocardial sclerosis and no evidence of rheumatic fever. Two lung biopsies showed pulmonary vascular changes compatible with those described by Parker and Weiss.[7] There was no calcification of the mitral valves and no left atrial thrombi.

Case Presentations.—

CASE 1.—D. M. was a 12-year-old white boy in whom a mitral diastolic murmur was first heard at the age of 2 months. His early years were characterized by limited activity and frequent respiratory infections. In the few years before operation he was tutored at home and had a progressively downhill course. He had had twenty-five hospital admissions for respiratory infections and congestive heart failure.

On admission to the Children's Medical Center, he had a respiratory infection and heart failure; present also were cardiomegaly, hepatomegaly, and clinical signs of severe mitral stenosis. He was placed in oxygen and treated medically very vigorously with diuretics, digitalis, antibiotics, etc. A right heart catheterization revealed an elevated pulmonary artery pressure (mean, 75 to 95 mm. Hg). Unfortunately a good pulmonary capillary pressure was not obtained. An attempt at left heart catheterization was contemplated but a small amount of general anesthesia dropped the blood pressure below 70 mm. Hg so that the plan was abandoned.

On Dec. 2, 1955, a mitral commissurotomy was done in the usual manner through a left fourth intercostal space incision. The pulmonary artery was large and turgid. Direct pressure readings revealed a PA pressure of 145 mm. Hg, left atrium pressure of 35 mm. Hg (mean), and left ventricular diastolic pressure of 12 mm. Hg (mean). This boy had a well-funnelled valve with a posterior opening not greater than 3 to 4 mm. in size. The commissures were quite well developed with thickening and fusion along the edges. The leaflets were quite supple. The valve was opened up to 2.5 cm. digitally and some anterior subvalvular stenosis also relieved. No obvious regurgitation was noted before or after the commissurotomy. No gradient could be demonstrated post-commissurotomy across the mitral valve, whereas there had been a 23 mm. Hg mean gradient before commissurotomy (Fig. 3).

This boy has been converted from a very restricted life in which even a few steps would cause dyspnea to one in which he goes to school, climbs stairs, walks a mile or two, and engages in mild athletic activities. Preoperatively he was hospitalized twenty-five times for heart failure and respiratory infections, and, in over 3 years since operation, he has not been hospitalized for these complaints.

CASE 2.—M. R. was a 6-year-old boy in whom a mitral diastolic murmur was discovered during a preschool physical examination. In the last year he had been somewhat restricted in activity and was tutored at home. He had had two or three bouts of dyspnea, cyanosis, and collapse often associated with anterior chest and upper abdominal pain. During his hospital stay he had numerous bouts of pulmonary edema and was very difficult to control on digitalis, diuretics, and salt restriction. The diagnosis of severe congenital mitral stenosis was made. Because of his precarious condition, a catheterization was not done preoperatively —the only patient of the 5 who did not have a preoperative study.

On Sept. 24, 1956, a mitral commissurotomy was performed, using a left fourth intercostal space approach. There was a 25 mm. Hg diastolic gradient at operation before enlarging the valve orifice and a residual 18 mm. gradient at completion of the operation. The valve was flat, thickened, and diaphragmatic. The opening was enlarged from 0.5 cm. to 1.5 cm. with the use of a guillotine knife. No commissures could be felt. There was shortening and thickening of the chordae tendineae. Since some regurgitation was being created, it was thought advisable not to enlarge the opening further.

This patient did well postoperatively and now goes to school. His activity has been much increased but he obviously now has some mitral regurgitation which limits him somewhat.

CASE 3.—S. H. was a 3½-year-old Negro girl who was a premature baby weighing four and one-half pounds. A mitral diastolic murmur was first heard at 3 weeks of age. During her first 2 to 3 years of life, this patient had repeated respiratory infections with questionable heart failure which required antibiotics and oxygen. At 3 years of age, she was digitalized. On admission to the hospital she appeared to be underdeveloped and chronically ill. She had both mitral diastolic and systolic murmurs at the apex; there was also hepatosplenomegaly. Right heart catheterization revealed a mean pulmonary artery pressure of 80 mm. Hg, a mean pulmonary capillary pressure of 29 mm. Hg, and a pulmonary vascular resistance of 9 to 10 units (normal up to 3 units). An electrocardiogram revealed right ventricular hypertrophy.

On Nov. 8, 1957, a mitral commissurotomy was performed through a left fourth intercostal space incision. The valve was diaphragmatic, thickened, and only slightly funnelled, with no obvious commissures. The opening was only 2 to 3 mm. in size and situated very

close to the mitral ring. The valve was opened with great difficulty, using the fifth finger, guillotine, and mitral dilators. Since some regurgitation was being produced, the valve was only opened to 7 to 8 mm. One had the impression that there was a mass of fused chordae tendineae beneath this opening.

This patient did reasonably well for 5 days postoperatively but suddenly died after finishing lunch. No postmortem examination was done. It was thought that aspiration of some food had occurred.

CASE 4.—J. K. was a 15-year-old white girl in whom a mitral diastolic murmur was first heard at the age of 9 months. Until the age of 13 years she had led a rather restricted life because of dyspnea, but at that time she had a spinal fusion performed for severe congenital lumbodorsal scoliosis. At the time of this operation she developed pulmonary edema. Because of her incapacity she was tutored at home. At the age of 15 years, a right heart catheterization showed a pulmonary artery mean pressure of 65 mm. Hg, a pulmonary capillary mean pressure of 27 mm. Hg, and a pulmonary vascular resistance of 9.0 units. Pulmonary function studies showed a restrictive deficit of 50 per cent. Because of her scoliosis no left heart catheterization was done. It was thought that the mitral stenosis was severe enough to warrant operation. She had no evidence of rheumatic fever in the past.

On Nov. 20, 1957, a mitral commissurotomy was performed through a left fourth intercostal space incision. The valve was diaphragmatic with firm thickened leaflets. There was a posteriorly placed 4 mm. opening and minimal evidence of commissure formation. There was no calcification or thrombus. The opening was enlarged digitally (fifth finger) up to 1 cm. but, because of the firm rubbery consistency, a guillotine knife was used to increase the opening to 2 cm. There was no obvious regurgitation before or after surgery but there was some fear that it might become a problem if any more enlargement of the orifice was undertaken. A diastolic gradient of 24 mm. Hg was measured across the mitral valve before the commissurotomy and an 8 mm. Hg gradient noted afterward. These were pressures taken at the time of surgery.

This patient did quite well immediately postoperatively. She eventually went to school rather than being tutored at home and was, in general, more active. She still is restricted and has some trouble from respiratory infections but seems to be better than preoperatively. It has been difficult to separate her cardiac from her pulmonary functional deficiency.

CASE 5.—F. B. was a 2½-year-old white boy who weighed five pounds and four ounces at birth. From the age of 2 months he had had repeated bouts of dyspnea and cyanosis with congestive heart failure which required six hospital admissions. A mitral diastolic murmur was heard at about 14 months of age and was accompanied by a mitral systolic murmur. On his last admission, at the age of 2½ years, he was in congestive failure with hepatomegaly, and right ventricular hypertrophy as disclosed by electrocardiogram and x-ray studies. A right heart catheterization revealed a pulmonary artery mean pressure of 45 mm. Hg and a left atrial pressure of 30 mm. Hg (catheter passed into left atrium via a small patent foramen ovale). His pulmonary vascular resistance was 4 units.

On Dec. 13, 1957, this patient was operated upon by way of a bilateral transsternal thoracotomy. The patient was attached to a pump-oxygenator. The heart was stopped with potassium citrate and the left atrium explored via the right atrium and interatrial septal approach. The mitral valve was somewhat funnel shaped with a centrally placed 5 mm. opening. There was some commissural definition. The valve was opened with scissors, anteriorly and posteriorly, up to 1.5 to 2 cm. The chordae tendineae were thickened, shortened, and fused. It was difficult to be sure just where the incisions should be made because of the subvalvular fusion and poor commissure formation. The left ventricle and atrium were filled with saline and the interatrial septum incision closed. The right atrium was closed and the aortic clamp released. The heart action returned but it was quite ineffective and, in spite of all efforts to resuscitate it, the heart finally stopped.

A postmortem examination revealed thickening of the left atrial endocardium, fusion and shortening of the chordae tendineae and papillary muscles. There was hypoplasia of the

left ventricle with some left ventricular outflow obstruction proximal to the aortic valve. The exact cause of death was not clear but it was thought that the additional load on the hypoplastic left ventricle might have been a factor.

CONGENITAL MITRAL INSUFFICIENCY

Two patients with congenital mitral insufficiency were operated upon within the last year. Neither of these patients represented the more common types of

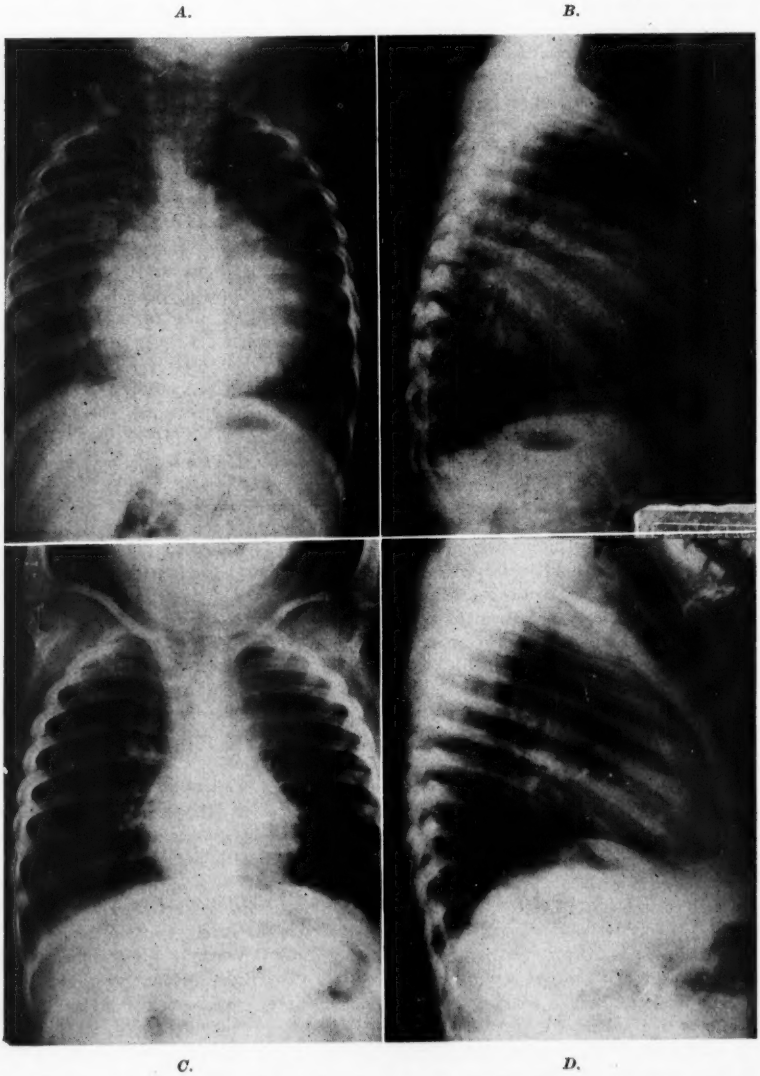

Fig. 4.—Preoperative (*A*, *B*) and postoperative (*C*, *D*) roentgenograms of Case 1 (P. B.). This patient had congenital mitral insufficiency.

congenital mitral regurgitation; that is, a cleft mitral septal leaflet associated with an ostium primum or atrioventricular canal, or the rarer absent or vestigial posterolateral mitral leaflet.[8] These 2 children, like the 5 previously described cases of congenital mitral stenosis, were very ill and doing poorly on a strictly supervised medical program. One of these patients was operated upon using an "open" method with the aid of a pump-oxygenator, followed by some improvement, and the second was operated upon using a "closed" method with an excellent result.

A brief summary will best bring out the salient features of these 2 unusual cases.

Fig. 5.—Congenital mitral insufficiency (Case 1, P. B.). Angiocardiogram from left femoral vein showing large pulmonary artery with no left branches, and a large left atrium.

Case Presentations.—

CASE 1.—P. B. was a 15-month-old, eighteen-pound, white boy admitted with cough, fever, cyanosis, and dyspnea. He had entered the hospital 4 months previously for investigation of his cough and dyspnea which were associated with mitral systolic and diastolic murmurs and a large left atrium. An attempt at right heart catheterization at this time was unsuccessful because of the onset of auricular flutter. On re-entry in July, 1958, he had a hacking cough, temperature of 102° F., pulse of 140, and a respiratory rate of 50. He was pale and cyanotic. He had an enlarged heart (Fig. 4), mostly left atrium, and a Grade 3 mitral systolic murmur with a questionable short diastolic rumble. Breath sounds were diminished on the left with hyperresonance on that side. The liver was down 4 cm. The patient was put on digitalis, oxygen, low salt intake, and antibiotics. He improved and was discharged only to return in August, 1958, at which time he was again cyanotic and pale, febrile, and in heart failure. He was treated vigorously, and again an attempt at right heart catheterization made. The mean pulmonary artery pressure was 42 mm.

Hg, pulmonary capillary pressure 22 mm. Hg (mean), and femoral artery pressure 95/47 mm. Hg (mean, 62 mm. Hg). The femoral artery oxygen saturation was 60 per cent, but with oxygen rose to 95 per cent. No shunt was demonstrated. An angiocardiogram (Fig. 5) showed a large pulmonary artery with a right branch but essentially no left branch. It also demonstrated a very large left atrium. The chest films over a period of several weeks had shown progressive diminution in the left pulmonary vascular markings accompanied by overdistention of the left lung. Eventually, the patient developed atelectasis, pneumonia, and fluid on the left side. The progressive loss of pulmonary vascular markings and subsequent

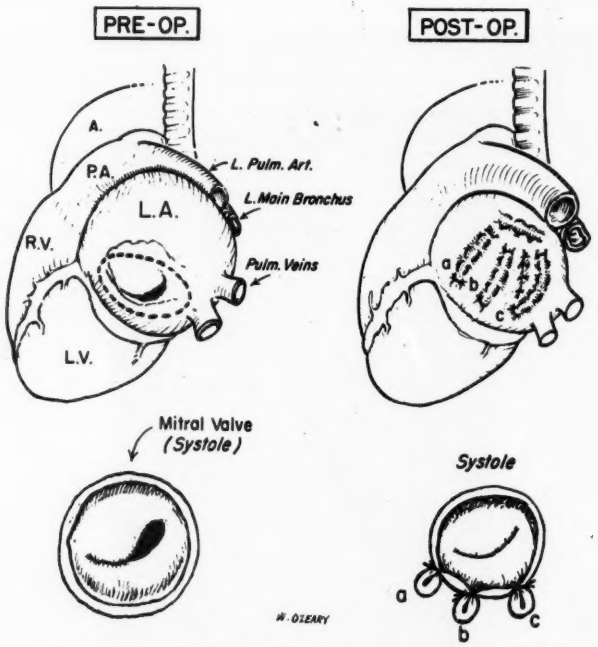

Fig. 6.—Repair of congenital mitral regurgitation. Preoperative view showing enlarged left atrium compressing left main pulmonary artery and bronchus. Postoperative view showing left atrium smaller and no compression of left main pulmonary artery and bronchus. Mitral ring sutures *a, b, c,* have now made the mitral valve competent.

atelectasis of the left lung were thought due to compression by the giant left atrium. Rivkin,[9] Murphy[10] and their associates have described this in the past. The diagnosis of congenital mitral insufficiency, possibly associated with some stenosis, was made. The posibility of a left atrial tumor or cor triatriatum was not ruled out but, because of the progressive downhill course of this child, he was taken to the operating room from the catheterization laboratory. He had a temperature of 103° F., pulse over 140, and atelectasis of the left lung the day of the operation. The white cell count was 27,000.

On Aug. 29, 1958, the patient was explored through a left fourth intercostal space incision. There was a considerable amount of clear yellow fluid in the left pleural space. The left upper lobe was atelectatic and pneumonic. The left lower lobe was almost totally collapsed. The heart was very large. The pericardium was opened and a moderate amount of fluid removed. The striking thing about the heart was the giant left atrium which was compressing the left main bronchus and pulmonary artery. On depressing the upper surface of the left atrium, the lower lobe immediately re-expanded and the left main pulmonary artery

distended. There was a readily palpable systolic thrill over the left atrium, particularly posteriorly and superiorly. There was a barely palpable diastolic thrill over the left ventricle. The main pulmonary artery was large and turgid. Both the right and left ventricles seemed hypertrophied.

The left atrium was entered through a large appendage. There was no tumor and no evidence of cor triatriatum. There was a very forceful systolic jet coming from a posteriorly situated, 1 cm., mitral valve opening. The mitral valve had a poorly formed anterior commissure and the valve itself was quite flat and taut; the valve ring seemed quite enlarged. The valve was opened up to 1.5 cm. and then 2-0 arterial sutures on large round needles placed through the left atrial wall and ring, guided by the intra-atrial finger. The needle was then guided out through the atrial wall and the suture tied. This seemed to make the ring smaller and so three or four such sutures were carefully placed near the left circumflex coronary

Fig. 7.—Congenital mitral insufficiency (Case 1, P. B.). Photograph made 8 months postoperatively.

artery and great cardiac vein. In this way several tucks were taken in the mitral ring posteriorly, laterally, and anteriorly. The systolic jet seemed to disappear. The sides of the tremendous left atrium were then reefed up as illustrated (Fig. 6) to make the left atrium smaller and thereby take the pressure off the left pulmonary artery and bronchus. The left lower lobe expanded well but the left upper lobe remained airless. Because it was a solid pneumonic lobe and a possible source of difficulty, it was quickly removed.

The patient did very well postoperatively and left the hospital on the eighth day following surgery—afebrile, acyanotic, off antibiotics, and with a normal white count. He has remained on digitalis. The left atrial appendage showed endocardial sclerosis and the left upper lobe demonstrated a chronic pneumonia but with pulmonary vascular changes compatible with the Parker-Weiss syndrome.

This boy was seen in April, 1959 (Fig. 7), 8 months postoperatively. He seemed perfectly healthy with a clear chest, normal-sized heart (see Fig. 4) and with Grade 1 mitral systolic and diastolic murmurs. He walks and runs, eats well, and weighs twenty-eight pounds, in contrast to his eighteen pounds at the time of operation. He has had no respiratory infections or difficulty since operation.

CASE 2.—R. F. was an 11-year-old white boy with a known mitral systolic murmur since the age of 9 months which was associated with cardiomegaly. For the past several years he had had many bouts of dyspnea, weakness, and occasional cyanosis. He also had many epistaxes but no local or systemic cause could be found. In June, 1958, he was admitted to the hospital in congestive heart failure. At this time he was digitalized and put on Diuril and a low sodium diet. He improved somewhat and was discharged. He returned again in September, 1958, having been markedly restricted in his activities. At this time he was leading a bed-to-wheelchair existence with minimal walking because of fatigue and dyspnea. It was thought at this time that he had dominant mitral insufficiency and some aortic and tricuspid insufficiency. He had no evidence of rheumatic fever at any time.

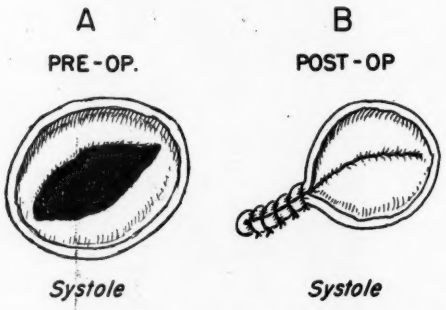

Fig. 8.—Surgical relief of congenital mitral insufficiency due to enlarged mitral ring (Case 2, R. F.). *A*, Preoperative view of valve in systole. *B*, Postoperative view of valve in systole, showing sutures in mitral ring over the posteromedial commissure.

A right heart catheterization revealed a low cardiac output, a pulmonary artery mean pressure of 47 mm. Hg, a pulmonary capillary mean pressure of 25 mm. Hg, and an aortic pressure of 88/65. There was also some suggestion of tricuspid regurgitation. The electrocardiogram showed left ventricular hypertrophy.

On Oct. 9, 1958, he was explored through a right fourth intercostal space incision. The heart was enlarged, particularly the left ventricle and left atrium. There was a systolic thrill over the left atrium and a lesser one over the right atrium. The patient was then attached to the pump-oxygenator after cannulation of the venae cavae and right subclavian artery. Just as the cannulation was being completed, the heart stopped but responded to intermittent compression and improved once the perfusion began. It was apparent that the left atrium remained full of blood and that the systolic jet, though less, was still palpable in the left atrium. A small incision was made into the left atrium, anterior to the right pulmonary veins, and a sucker inserted. It was obvious that the left atrium was being rapidly filled from the left ventricle due to the aortic regurgitation. Because of this, the ascending aorta was clamped above the coronary arteries and the left atrium then collapsed and became dry. The heart was then stopped and the left atrium opened widely. The mitral ring was very large. There was no slit in either leaflet of the mitral valve, nor was there any rupture of the chordae tendineae. The leaflets were somewhat thickened and very pale, suggesting endocardial sclerosis. The enlarged ring was therefore made smaller by inserting six 2-0 arterial sutures into the ring on either side of the posterior commissure (Fig. 8). These were

then tied until the leaflets seemed to approximate each other. The orifice was diminished from at least three fingers to just a bit less than two fingers. This procedure seemed to make the rather flattened valve more funnel shaped. The somewhat thickened and taut chordae tendineae were also more relaxed. The left side of the heart was then allowed to fill with blood and the atriotomy closed. The aortic clamp was released and the heart started sluggishly but soon resumed a normal sinus rhythm. The systolic thrill was not palpable over the left atrium at a systemic blood pressure of 85/68. The right atrial systolic thrill remained about the same. Because of the long procedure and precarious condition of the patient, no direct investigation of the aortic or tricuspid valves was attempted.

The patient's early postoperative course was stormy but he eventually improved and was discharged—15 days after his operation. Follow-up visits have shown some diminution in the heart size (Fig. 9), particularly of the left atrium. Both the patient and his parents feel that his exercise tolerance has improved. He still has an aortic diastolic murmur and some mitral insufficiency by auscultation. Six months postoperatively he is able to go up a flight of stairs, sleeps flat, plays basketball, and rides a bicycle. He could do none of these things preoperatively.

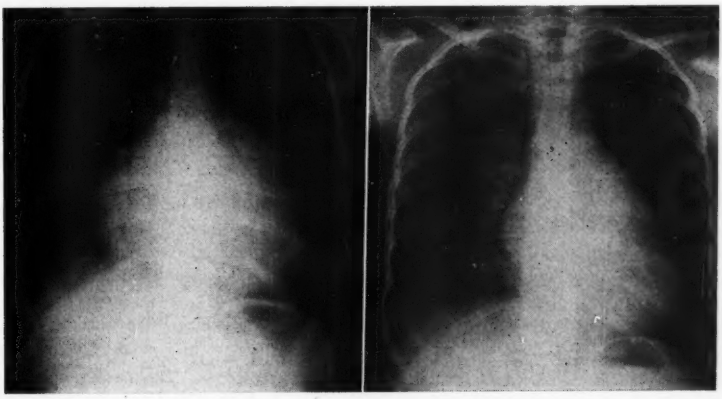

Fig. 9.—Congenital mitral insufficiency (Case 2, R. F.). *A*, preoperative roentgenogram which shows large left ventricle, left atrium, and pulmonary arteries. *B*, Postoperative roentgenogram (6 months) which shows diminution in size of left ventricle, left atrium, and pulmonary arteries.

DISCUSSION

Congenital mitral stenosis is a rare cardiac anomaly and carries a grave prognosis. It is not too difficult to recognize by simple clinical and laboratory methods. It is characterized by the early onset of a mitral diastolic murmur and evidence of pulmonary arterial and left atrial hypertension. Pathologically there appears to be a broad spectrum of findings beginning on the one extreme with a flat, thickened, diaphragmatic valve with little or no commissural formation, with short fused chordae tendineae, to the other extreme where one finds a well-funnelled valve with fused, well-formed commissures and fairly supple leaflets. The degree of endocardial sclerosis or subendocardial fibroelastosis seems greater in the first-described or more primitive-type valve and less pronounced in the more nearly normal-appearing valve. Since the prognosis is

so poor in this condition, it would appear that surgery should be given a fair trial. Whether an "open" or a "closed" method should be used still remains unsettled.

Congenital mitral regurgitation not associated with an ostium primum defect or atrioventricular canal defect appears to be an even rarer lesion. In these 2 reported cases, dilatation of the mitral ring was the dominant feature. An "open" method of surgical approach would seem to give greater latitude in the type of repair for this defect.

SUMMARY

Five cases of congenital mitral stenosis treated surgically are reported. The clinical, pathologic, hemodynamic, and surgical aspects of the problem are discussed. There were four "closed" type operations with one death. In the 3 survivors, there was one excellent result and two fair to good results. A fifth patient was operated upon with the use of a pump-oxygenator but died at the end of the procedure.

Two patients with congenital mitral insufficiency were operated upon with no deaths. One had an excellent result and one a good result.

These two congenital mitral valve anomalies appear to be rare and carry a very poor prognosis. It is suggested that this diagnosis be more seriously entertained in the future and that surgical intervention be undertaken in these seriously ill children.

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DISCUSSION

DR. WILLIAM H. MULLER, JR., Charlottesville, Va.—Congenital mitral stenosis is indeed a relatively rare malformation which presents a real problem when it is encountered. I am very pleased to have had an opportunity to hear Dr. Starkey's interesting presentation this morning.

When we have operated upon patients with congenital mital stenosis, using a closed method, mitral insufficiency invariably resulted. The first patient on whom we performed an open operation, utilizing the pump-oxygenator, had a diagnosis of corrected transposition of the aorta and pulmonary artery and congenital mitral stenosis. We found a situation similar to that which Dr. Starkey described; that is, a narrowed valve in which no commissural fusion lines could be seen. Incisions were made in the valve approximately where we thought the commissures should be. This child likewise did not survive the procedure. More recently, however, we have operated upon a patient in whom Dr. Frank Dammann made a diagnosis of isolated mitral stenosis. We found, just as Dr. Starkey did, that there was thickening of the valve and shortening and fusion of the chordae tendineae. Incisions were therefore made into the valve leaflets opposite the chordae attachments and the papillary muscles were split down to their bases. The incisions were made actually into the anterior leaflet of the mitral valve.

One can make three incisions: we made only two in this patient, but obtained what we thought was a normal-sized mitral valve. This patient had no resultant mitral insufficiency, and has made an uneventful recovery and is greatly improved. We think therefore that the incisions should be made through the valve leaflet, chordae tendineae and papillary muscles rather than where one thinks the commissures should be in this type of mitral stenosis.

DR. GEORGE A. CLOWES, JR., Cleveland, Ohio.—I, too, greatly enjoyed Dr. Starkey's excellent presentation.

I would like to say a word about the matter of the approach to the mitral valve by open surgery. Before at these meetings we have heard remarks by Dr. Lillehei, Dr. Kay, and others. All of these authors have recommended the right-sided approach to the mitral valve for open surgery. I would just like to give you a little of our experience in approaching it from the left side.

(Slide) This is done by cannulating externally, as you see here, the inferior vena cava through the saphenous orifices into the femoral veins and inferior vena cava, through the internal jugular vein and down into the right heart. A ligature is placed around the pulmonary artery excluding the left side from the circulation. Perfusion is continued through the femoral artery.

We have had experience with 8 cases in this fashion. Most of them have been mitral insufficiency. We have had one death and four very satisfactory results. That is not the point. The thing is that the left-sided approach does, in my opinion and in the opinion of those of us who have worked with it, have some advantages.

First of all, with the patient tipped 'way up on his right side, almost over toward the face-down position, the mitral valve becomes the highest point in the ventricle, and therefore any air that is trapped is expelled through it rather than into the aorta, avoiding air embolus. There is one point I would make before leaving this slide. That is, one must thread this catheter down into the right ventricle before occluding the pulmonary artery, to avoid distention of this chamber, otherwise failure will result. This was the cause of the death I mentioned.

This slide shows the exposure of the mitral valve that was obtained in a 14-year-old girl through the left-sided approach. In our experience this is much easier than the approach through the right side, in that the valve is much closer to one and easier to work on.

This slide shows the valve of another patient who was operated on by this technique, a 53-year-old woman.

This slide shows her appearance postoperatively. I think we will leave the rest out.

Dr. Cross, last year at this meeting, described his experiences with operating on dogs in the right- and left-sided approach. He stated that from the right side he had less air embolus. Our experience has been different from this. We find that this matter of placing the mitral valve highest in the heart is of some importance in this regard.

Thank you very much. I take this opportunity again to say how much I have enjoyed Dr. Starkey's nice presentation, and hope that perhaps this technique may be of some use to some of you.

DR. CHARLES P. BAILEY, Philadelphia, Pa.—I very much enjoyed this talk of Dr. Starkey's because we have had a somewhat similar experience.

Actually, I have operated on only 4 children with congenital mitral stenosis. The pathology is distinctly different, of course, from that in the rheumatic case, and indeed doesn't have to follow any particular pattern at all.

All of mine were operated by the closed technique, 3 from the left side with one resultant insufficiency, 1 from the right side. I did not manage to separate the valve adequately on that last occasion, because the papillary muscles grew fast to the undersurface of the valve and I was unable to cut them with the closed technique. That child will be brought back shortly for an open operation.

I believe that the variances in this pathology strongly demand the open technique, which I am sure Dr. Starkey will and should continue to use. And I would like to point out that whereas we use the right-sided approach for all of our closed operations on the mitral valve, the experiences of my associate, Dr. Henry Nichols, in operating for mitral insufficiency have clearly demonstrated the advantages of the left-sided approach when the open technique is used. Indeed, Dr. Clowes already has pointed out the major advantages, perhaps the most major being the surgeon's ability to remove entrapped air from the ventricle, thus preventing air embolism. It is inevitable that air will enter the left ventricle with an open operation for mitral stenosis.

The real difference in the right- and left-sided approach lies in the difference in the direction of the line of the valve. If you can see it you can easily orient yourself, whether it runs vertically or whether it runs horizontally. The advantage with the right-sided approach in closed operations for mitral stenosis is that the valve presents as an upright "U," whereas from the left-sided approach it lies at a right angle, thus tending to confuse the surgeon and restrain his aggressiveness.

It was a real privilege to hear this very excellent paper.

DR. FREDERICK S. CROSS, Cleveland, Ohio.—Perhaps I am somewhat out of order arising to discuss a previous discussion, but I think there is something extremely important about the approach to the mitral valve, whether it be from the right or left side, that should be emphasized further, and that is the problem of trapped air in the left ventricle.

Last year, in a discussion of one of the papers before this organization, I pointed out in a series of slides that in our opinion, based on both laboratory and clinical experiences, there is less chance for air to be trapped in the left ventricle when the mitral valve is approached from the right side than from the left. Anatomically, the left ventricle is the dependent chamber when the patient is on the operating table with the right side up. Unfortunately, when the valve is approached from the right side, it may be more difficult to work on since the surgeon finds himself somewhat further from his work.

Much of this discussion may be a little beside the point, however, since uniform successful results will be obtained only when one develops that technique which works best in his own hands. The real point of this discussion is that regardless of the approach to the mitral valve, it is extremely important as an added precaution to vent the left ventricle. This vent is kept on gentle suction until the left atriotomy is repaired and the vena caval tapes released to be sure that all residual air bubbles in the left ventricle are removed before turning off the pump-oxygenator and allowing the heart to take over its own function. This maneuver will be a virtual guarantee against air emboli arising from residual air in the left ventricle.

I would like to congratulate the authors on an excellent presentation of an important piece of work, and I appreciate the opportunity to discuss this one important aspect of it.

DR. ROSS ROBERTSON, Vancouver, British Columbia.—Dr. Starkey's paper has interested me immensely. It reminded me of the case of a young woman with a congenital mitral stenosis who survived this lesion, generally lethal to children, because of an associated left superior vena cava emptying into the left superior pulmonary vein. This relieved her mitral

stenosis as does the Sweet operation for acquired mitral stenosis. Clinically she was short of breath on mild exertion. There was a continuous murmur over the second left interspace close to the sternum, and also a mitral diastolic murmur.

At operation, the blood could be seen in the distended thin-walled left superior vena cava, flowing away from the heart. When the left superior vena cava was clamped, the pressure rose alarmingly in the left auricle, confirming the preoperative diagnosis of mitral stenosis. Consequently, a finger was inserted into the left auricle and found a valve which resembled that described by Dr. Starkey, a kind of membrane with a hole in the middle and no actual commissure. A knife was required to open the valve along a line where the commissures should be located. A mild mitral regurgitation was produced. The left superior vena cava was then clamped without causing an increase in pressure in the left auricle. The clamp was then removed.

The patient made a good recovery and is free of symptoms.

DR. EDOUARD D. GAGNON, Montreal, Quebec.—I think Dr. Starkey's paper was an excellent one.

I do not wish to discuss points of technique, but I would like to ask him a question on the definition of a congenital mitral stenosis. I ask this question because in the beautiful slide he showed us he had three diaphragmatic stenoses, one of which was slightly funneled and one well funneled, but he showed us, and stated, that they were all *thick* valves.

We have operated on 6 children and 2 of them had these thick valves. Although they had no history of rheumatic fever, we felt that they were acquired, probably due to some other infectious process in childhood. In opposition to these 2, the other children we had to operate on (2 of them with associated coarctation) had valves that were quite different. The leaflets were not thickened at all; there were no commissures that I could recognize. There was a long funnel-shaped affair with very short chordae tendineae, inserting right down near the apex of the ventricle. We cut where we thought the commissures should be and the 4 patients did well. The oldest patient we operated upon was 14 years and the youngest was 8 years of age.

We feel that these 4 are the real congenital type, and that the first 2, of the type shown here, were probably acquired, although we couldn't determine what the infectious process was that had scarred the valve leaflets to produce the mitral stenosis.

DR. H. WILLIAM SCOTT, JR., Nashville, Tenn.—I, too, would like to congratulate Dr. Starkey on bringing this extremely interesting and important problem before the Association. I think it has been the feeling of almost everyone, both internists and surgeons alike, up until very recently, that congenital mitral stenosis represented a relatively hopeless problem from the therapeutic point of view. This had certainly been my understanding.

We have had an opportunity to operate definitively on only 1 patient with congenital mitral stenosis. The nature of the anatomic deformity of the valve was the problem that seemed to us most intriguing, in addition to the question as to whether this might be an acquired lesion of rheumatic origin rather than a congenital one.

Our patient was a 6-year-old child with symptoms from birth, a classical presystolic rumbling murmur at the apex and severe pulmonary hypertension. We did the operation using the open technique with the pump-oxygenator, and had an opportunity to see that the little valve resembled one of the diagrams shown us by Dr. Starkey.

At operation, with the valve exposed, I wanted to find out what the valve felt like, and I used what I thought was very gentle pressure with a finger, simply to assess the edges of the stenotic valve, and I found that the commissures were opened completely simply by the gentle palpation of the operating finger.

We then carefully inspected the little valve and it seemed that what we had divided by digital pressure was a diaphanous membrane with a little slit in it that seemed to fill the orifice between the anterior and posterior leaflets. The valve was otherwise quite normal, as best we could tell, with no evident thickening of it.

I think it would be interesting if Dr. Starkey could bring out to us in his closure of discussion some idea of the anatomic variations of the valve in congenital mitral stenosis, because I think the type of operative procedure that one plans or that one may do should be totally dependent upon the anatomic deformity of the valve.

Our little patient has done fairly well in the 6 months since operation despite a hypoplastic left ventricle, but has not yet had postoperative catheterization studies.

DR. STARKEY (Closing).—I would first like to thank the discussers for their comments and will try to answer some of their inquiries.

As far as the anatomy of congenital mitral stenosis is concerned, there is great variation. It would appear, though, that a considerable degree of subendocardial fibroelastosis is associated with the flat, diaphragmatic type of valve with short or poorly developed chordae tendineae and papillary muscles. This may be associated with considerable hypoplasia of the left ventricle.

The etiology of congenital mitral stenosis is unknown. Fetal endocarditis has been postulated, but I am afraid I have nothing to contribute to this phase of the problem.

The question of surgical approach has been raised by several discussers. I think that for most cases of stenosis or insufficiency that an "open heart" method using a pump-oxygenator is preferable. We favor the right-sided approach to the left atrium. This chamber may be approached satisfactorily either directly anterior to the right pulmonary veins or by way of the right atrium and the interatrial septum. Each method has given an excellent view of the mitral valve.

The child with congenital mitral stenosis who reaches the age of 10 or 12 years seems more likely to have a valve that is funnel-shaped with fused commissures like those of rheumatic mitral stenosis. These are often amenable to surgical relief by the standard, left-sided closed method that one uses routinely in the adult rheumatic patient.

THE ETIOLOGY AND PREVENTION OF ATRIAL FIBRILLATION AFTER MITRAL VALVOTOMY

C. Frederick Kittle, M.D., and James E. Crockett, M.D. (by invitation), Kansas City, Kans.

THE MOST frequent postoperative complication following mitral valvotomy is the occurrence of atrial fibrillation in a patient with previously normal sinus rhythm. This postoperative complication is of particular interest to those concerned with cardiovascular surgery since this arrhythmia may lead to a deleterious tachycardia and a significant reduction in cardiac output. We should like to review our experiences with postoperative atrial fibrillation in 254 consecutive patients undergoing mitral valvotomy with particular emphasis on the prevention of this arrythmia.

DATA

The clinical records of all patients undergoing mitral valvotomy at the University of Kansas Medical Center and the Kansas City Veterans Administration Hospital since 1953 have been included in this study. Excluded are those in whom operative or postoperative fatality occurred or in whom records are incomplete. This group consists of 254 patients.

Of these 254 there were 99 (39 per cent) who had atrial fibrillation preoperatively and 155 (61 per cent) with a normal sinus rhythm preoperatively. Of the 155 patients, there were 41 (26 per cent) who developed atrial fibrillation postoperatively, this being the most common postoperative complication noted with this surgical procedure.

Atrial fibrillation in the 41 patients developed as early as the operative day (3 patients) and as late as the fifteenth day, although the majority had the onset of this arrhythmia between the second and fourth postoperative days (Fig. 1). No obvious correlation was found between the age of the patients and those in whom fibrillation occurred. The youngest patient was 16 and the oldest was 55 years with a mean age of 38.

It is of interest that 40 of the 41 patients who fibrillated postoperatively had dynamic mitral stenosis as their main lesion, although several other patients in our series had a normal sinus rhythm and at the time of cardiac exploration

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Supported in part by the Kansas Heart Association and the National Heart Institute.

Read at the Thirty-ninth Annual Meeting of The American Association for Thoracic Surgery at Los Angeles, Calif., April 21-23, 1959.

were found to have predominantly mitral regurgitation. The 1 patient who did fibrillate with mitral regurgitation was a 16-year-old girl who developed acute rheumatic fever postoperatively and died several weeks later.

The 155 patients with a normal sinus rhythm preoperatively have been divided into four groups: (1) those receiving both digitalis and quinidine, (2) digitalis alone, (3) quinidine alone, and (4) those receiving neither digitalis nor quinidine. Of those receiving digitalis and quinidine the smallest percentage of patients developed atrial fibrillation after operation—9 of 55 patients or 16 per cent. In the group receiving digitalis alone, there were 13 of 43 patients or 30 per cent. In the group receiving quinidine alone, there were 7 of 20 patients or 35 per cent, and in those receiving no medication 12 of 37 patients, or 32 per cent, developed atrial fibrillation.

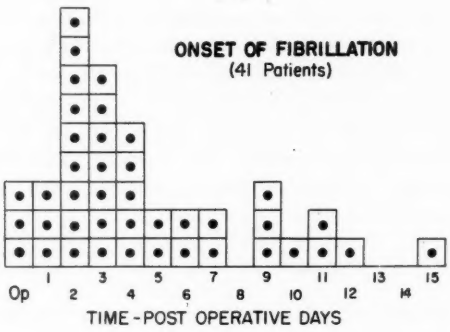

Fig. 1.

In the group of 55 patients receiving both digitalis and quinidine postoperatively as prophylaxis against fibrillation, there were 9 patients who developed fibrillation. In reviewing these particular instances, only 3 were given quinidine judged adequate by our present standards. Although 2 received 0.4 Gm. every 4 hours and 1 received 0.3 Gm. every 4 hours, fibrillation still occurred. The remaining 6 patients were given comparatively meager doses of quinidine, 0.2 Gm. four times daily or 0.2 Gm. every 4 hours.

Of 98 patients who were digitalized postoperatively, 22 fibrillated, an incidence of 22 per cent. Of the 57 patients not digitalized, 19 fibrillated, an incidence of 33 per cent. Thus, the value of both digitalization and quinidinization to prevent postoperative fibrillation would appear substantiated by these statistics.

In the 41 patients who developed atrial fibrillation, there were 3 patients who converted to a normal sinus rhythm spontaneously. These 3 are of considerable interest because their fibrillation began on the operative day, the first postoperative day, and the twelfth postoperative day following an esophagoscopy. Fibrillation in this particular group of 3 patients occurred at unusual times in comparison to other patients who fibrillated. In 5 other patients, no attempt was made to convert the fibrillation to a normal sinus rhythm because of factors which contraindicated quinidine therapy.

In 33 patients an attempt was made to convert the atrial fibrillation to a normal sinus rhythm. In 28 instances this was successful and in 5 it was unsuccessful. Of the 28 who were converted, this was accomplished by quinidinization in 15 patients already digitalized. In 6, conversion was by quinidinization alone, in 5 by postoperative digitalization or extra digitalis, and in 2 by Pronestyl and digitalis. It is believed quite important to convert patients with postoperative atrial fibrillation to a normal sinus rhythm if this can be accomplished.

In the 99 patients who underwent mitral valvotomy with preoperative atrial fibrillation, an attempt to convert to a normal sinus rhythm was made postoperatively in 45. Of these, only 12 were successfully changed to a normal sinus rhythm. Attempts to convert such patients prior to mitral valvotomy have not proved worth while.

DISCUSSION

Atrial fibrillation is a sufficiently common complication of mitral valvotomy to warrant particular attention to its prevention and correction. In a recent article, Heinz and Hultgren[10] reported that 47 per cent of patients undergoing mitral valvotomy with preoperative normal sinus rhythm developed atrial fibrillation postoperatively. In other reviews the incidence has varied from 24 to 38 per cent.[6, 8, 15, 19, 23] Most of the patients described in these articles received digitalis but no quinidine postoperatively.

Atrial fibrillation is a relatively uncommon complication in other postoperative patients who do not have chronic rheumatic heart disease, although it is occasionally seen following thoracotomies. After lobectomy or pneumonectomy in older patients, an incidence between 3.5 and 14 per cent has been noted.[1, 5, 10, 13, 16] In patients who had an intrapericardial pneumonectomy, an incidence of 45 per cent was found by Hurt and Bates.[11] It is significant that only 6 of 43 patients in this study who received quinidine after intrapericardial pneumonectomy developed atrial fibrillation, while 10 of 22, who did not, maintained sinus rhythm. Atrial fibrillation is relatively infrequent following operations for congenital heart disease.

Reasons for the development of postoperative atrial fibrillation after mitral valvotomy are not clear. Trauma to the left atrium with subsequent edema and tissue necrosis incident to the valvotomy must be considered an important factor. Others have mentioned the possibility of traumatic pericarditis or postoperative alterations in serum and intracellular electrolytes, but data do not confirm these as etiological factors.[10]

Rheumatic activity as evidenced by histologic findings in the resected atrial appendage has not been found significant in postoperative atrial fibrillation.[6, 10] In our group of 41 patients, the dynamic lesion in 40 was mitral stenosis, although others[10] have stated that atrial fibrillation occurs with greater incidence in patients with mitral regurgitation.

Postoperative atrial fibrillation is a primary concern because of its potential and real danger to the patient.[18] There are many studies to demonstrate that atrial fibrillation significantly reduces the cardiac output.[2, 3, 20-22]

Hansen and his associates[9] found a decrease of 23 per cent in cardiac output in patients with onset of atrial fibrillation. These patients had well-controlled ventricular rates before and after atrial fibrillation, thus eliminating the variant of ventricular rate as a factor in cardiac output. Conversion to a normal sinus rhythm reduced the pulmonary blood volume and the peripheral venous pressure.

Similarly, Kerkhof[12] found atrial fibrillation to reduce cardiac output by 25 per cent. Corday and his co-workers[4] reported a substantial fall in cardiac output and coronary blood flow with atrial fibrillation. This rapid and appreciable reduction in cardiac output appears the most serious effect of atrial fibrillation. If the ventricular rate reaches 130 to 150 per minute, the cardiac output is even more seriously compromised. Landis and his co-workers[14] have found a disproportionate rise in central venous pressure in dogs after atrial fibrillation began.

In several patients in our group of those who developed postoperative fibrillation, definite evidence of pulmonary edema was noted soon after onset of the atrial fibrillation. The possibility of thrombus formation and embolism would appear increased although we have not observed this.

A considerable difference of opinion exists regarding the role of quinidine in the prevention of postoperative atrial arrhythmias. It is generally conceded that digitalis is of most importance in decreasing and controlling ventricular rate if atrial fibrillation does occur. However, there is no general agreement that digitalis prevents postoperative atrial fibrillation. Wood[23] and Goodwin[8] have expressed the opinion that quinidine is of no value in avoiding this arrhythmia. We believe that combined digitalization and adequate quinidinization are definitely indicated for the prophylaxis of postoperative atrial fibrillation. In our study, those patients receiving both drugs postoperatively had an incidence of atrial fibrillation of only 16 per cent as compared to 30 per cent for those receiving digitalis alone, 35 per cent for those receiving quinidine alone, and 32 per cent for those who received neither drug. The difference among the last three groups are not statistically significant. As noted previously, the majority of those receiving quinidine alone or with digitalis received small amounts of the drug. We now believe that adequate quinidine prophylaxis requires 0.4 Gm. every 4 hours or 2.4 Gm. each 24 hours. This dosage requires daily monitoring by the electrocardiogram, observation of the blood pressure and, when available, serum quinidine levels (Fig. 2).

Conversion of postoperative atrial fibrillation to normal sinus rhythm is much easier than is the conversion of chronic fibrillation. We were able to convert 84 per cent of those with postoperative atrial fibrillation, but only 26 per cent of those with chronic fibrillation. Sellors[19] converted only 1 of 41 with chronic fibrillation while Wood[23] reported a 50 per cent conversion rate in this group although he noted that 40 per cent of these later relapsed to atrial fibrillation.

We have preferred to wait until after the tenth postoperative day to attempt conversion. This allows for healing of the atriotomy and general recovery of the patient. An attempt is made postoperatively to convert all patients to a normal sinus rhythm. To date we have not observed peripheral embolization occurring with or after restoration of sinus rhythm. In patients in whom left atrial thrombus is found that cannot be removed by the usual operative procedure, a re-operation is done utilizing extracorporeal circulation. Following this, when the atrium has been thoroughly cleaned of thrombus, the conversion attempt is made.

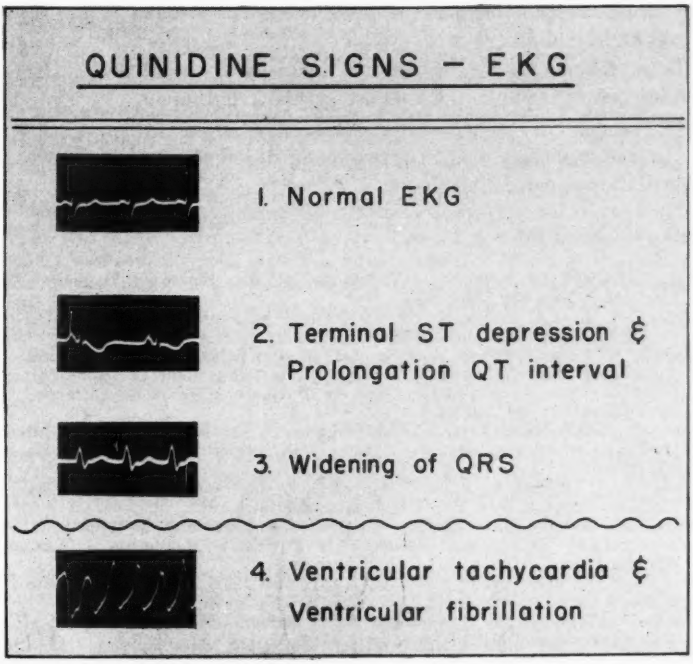

Fig. 2.

In those patients in whom postoperative fibrillation has occurred, quinidine is continued for several weeks with a gradual reduction in dose after dismissal from the hospital. Sudden termination of this drug from a high dosage level may result in a return to atrial fibrillation. In chronic fibrillation, the quinidine is continued indefinitely if conversion to a normal sinus rhythm has been accomplished. The maintenance dose is arbitrarily determined from the amount required to effect conversion and the patient's tolerance. Maintenance therapy is necessary to prevent recurrent atrial fibrillation.

SUMMARY

1. Two hundred and fifty-four consecutive patients who had mitral valvotomy are reviewed with particular attention to atrial fibrillation as a postoperative complication.

2. Atrial fibrillation occurred postoperatively in 41 of 155 patients (26 per cent) who had a normal sinus rhythm preoperatively.

3. The arrhythmia developed most commonly on the second, third, or fourth postoperative day.

4. The frequency of postoperative atrial fibrillation was significantly lower in those patients receiving both digitalis and quinidine postoperatively. It is concluded that the combined use of these drugs is beneficial in preventing this deleterious arrhythmia.

5. Local trauma to the left atrium incident to the atriotomy is probably the most important factor in the etiology of this arrhythmia.

6. Conversion of postoperative atrial fibrillation to sinus rhythm can usually be accomplished while conversion of those patients with preoperative atrial fibrillation is more difficult.

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Discussion

DR. HARRISON BLACK, Boston, Mass.—I have enjoyed Dr. Kittle's discussion very much. It was of interest to me to find this work on the program because we have analyzed some of our experience with this problem in the cases at the Peter Bent Brigham Hospital in Boston.

(Slide) I might say at the outset that I am alarmed at the size of the quinidine doses employed by Drs. Kittle and Crockett. It is well known that the blood level obtained on similar dosage varies widely from patient to patient and that even with the total daily dose of 1.2 Gm. serious toxicity and even death has occurred. This is only half the dose used in many of Dr. Kittle's patients. We have employed two regimens, one with a total daily dose of only 0.8 Gm. daily and the other 1.2 Gm. The important point that I would like to make is that, with such doses, results equally as good as those of Drs. Kittle and Crockett can be obtained. I sincerely believe that the higher doses employed by them need not and should not be used.

In our study we divided our patients according to our usual clinical classification of mitral stenosis. In Group III of 230 patients who were treated with quinidine, 50 fibrillated, an incidence of 22 per cent, as contrasted with 42 per cent in the controls. This is significant at the 0.1 level of confidence. In Group IV, however, the use of quinidine reduced the occurrence of postoperative atrial fibrillation only from 62 to 50 per cent—not a significant difference.

We also analyzed some of the factors that we thought might have a bearing on the development of this arrhythmia postoperatively, analyzing controls and quinidine patients separately. In the control group, there was a significantly higher incidence of fibrillation when there had been prior atrial fibrillation, atrial premature beats, or episodes of palpitation preoperatively. The finding of Aschoff bodies in the auricular appendage biopsy and moderate or marked post-fracture mitral insufficiency also had a statistically significant influence on the incidence of fibrillation. Recent arthralgia as evidence of rheumatic activity was not statistically important.

In the quinidine patients, however, only one of these factors—prior atrial fibrillation, atrial premature beats, or episodes of palpitation—seemed to have any significant influence.

As far as quinidine blood levels were concerned, there did not seem to be any important difference between those who fibrillated and those who did not. On the first postoperative day those who fibrillated had an average level of 4.61 gamma while those who remained in normal sinus rhythm had an average value of 4.44. Blood levels taken as soon after the onset of atrial fibrillation as possible were even higher (average 5.92) so that this factor is obviously not of critical importance.

Summing up, we can say that, in Group III patients undergoing mitral valvuloplasty, quinidine reduces the incidence of postoperative atrial fibrillation in our experience from

42 to 22 per cent. Of those who fibrillate, 36 per cent will revert spontaneously when their rate is slowed by increasing digitalis dosage. (I should mention parenthetically that it is our practice to digitalize all patients before mitral surgery and carry them on maintenance digitalis postoperatively.)

Of those who do not revert spontaneously, 89 per cent can be reverted with quinidine in about 10 days after operation. Therefore, if we start with 100 patients who are in normal sinus rhythm, who are digitalized and on quinidine preoperatively, there will be postoperative fibrillation in 22, spontaneous reversion in 8. Of 14 who remain in atrial fibrillation, 12 can be reverted and only 2 will leave the hospital with an irregular rhythm.

DR. JEROME R. HEAD, Chicago, Ill.—Dr. Kittle's very interesting paper has interested me, although I am not a cardiac surgeon, as I am sure it has interested everyone who is a cardiac surgeon and is a thoracic surgeon.

We have had, after pneumonectomies and lobectomies, our share of postoperative fibrillations. We have come to be able, I believe, to anticipate them. In older people, whose coronary circulation is poor, we use quinidine prophylactically.

There is one point in the etiology that I would like to bring up, and that is why I am discussing this paper. That is the importance of adequate respiratory toilet after surgery, and of an ample supply of oxygen. In 1 patient who fibrillated after surgery and did not raise his secretions and became progressively worse, we did a tracheotomy and put him on a pump respirator. As we slowed down the respirator we could make him fibrillate; as we speeded up the respirator the fibrillation would stop.

This led us to what seems to me to be a very reasonable conclusion, that the oxygen in the blood plays an important part in postoperative fibrillation. Since that time we have been able to convert a number of patients with postoperative atrial fibrillation simply by using a nasal catheter and cutting down their activity.

DR. LAURENCE K. GROVES, Cleveland, Ohio.—We have not used the prophylactic quinidine, but I believe we use quinidine postoperatively about as has been shown. I am neither a cardiologist nor a pharmacologist, but little mention was made of the toxicity of quinidine. Down on the bottom of the last slide there was a little comment about ventricular arrhythmias, and I am sure that with the help of our cardiologists we have killed at least 1 patient by steadily increasing the dose in refractory fibrillation postoperatively. Nothing was found in this gentleman at postmortem after being found dead in bed, but I presume that he had ventricular fibrillation.

DR. MAX G. CARTER, New Haven, Conn.—Like the last discusser, I come merely because I am trying to learn.

Our cardiologists are at the moment rather insistent that we not give prophylactic quinidine, and I would like to ask Dr. Kittle about this problem. Some years ago we felt that people with arteriosclerotic heart disease, who were going to have esophagectomies or pneumonectomies, should have prophylactic digitalis and we used it and had very few arrhythmias. We have since stopped that, and I am sure we don't have any more arrhythmias than formerly.

In the cardiac patients, however, digitalis is given only when there is a specific indication, and in the patients who come to operation with a normal rhythm, if there is not an indication, digitalis is not given. If they then begin to fibrillate, digitalis is given with a view to getting them fully digitalized within the first 24 hours. If they do not convert, then quinidine is added immediately.

This has seemed reasonable to me purely on the advice of the cardiologists. They point out, I think correctly, that digitalis and quinidine are both toxic drugs, and, in some of these patients who have a markedly impaired myocardial reserve, one may get into more trouble using it than in not using it.

We have had a lot of experience demonstrated this morning, and I would like to hear how Dr. Kittle feels about this problem.

DR. CHARLES P. BAILEY, Philadelphia, Pa.—I wasn't going to join the discussion, but I feel so strongly about digitalis that I thought I should.

Our cardiologists for a long time had the same feeling as Dr. Carter: "There is no use in giving digitalis unless there is impending heart failure, auricular fibrillation or something of that sort." The trouble is, they forget that we in our surgery often produce heart failure, or so reduce the reserve of the heart that it is practically in failure. That is when the patients need the digitalis. If you have not given it in advance you then have to give it intravenously. It then takes 20 minutes, which may be too long.

We have had to use ouabain and other rapidly acting glucosides to save some of these people right under our eyes during open-heart surgery. There is no question but that some of the hearts just would not beat effectively and that they could not be taken off the pump until these glucosides took effect. We are convinced of the great value of "prophylactic" digitalis in all patients undergoing any kind of heart surgery. This has been substantiated in many laboratories in experimental work in animals, the results showing a much higher survival rate in certain operations on the heart when digitalis is used routinely than when it is not. We ought to take advantage of our animal experiences and bring clinical medicine at least up to the experimental level.

DR. KITTLE (Closing).—I am grateful to all of the discussers for their remarks. I think postoperative atrial fibrillation is an extremely important problem. Because of the wide variety of patients who are being subjected to operation, this is a problem that can be settled only by a careful statistical analysis of large series. The more critical appraisal there is in each particular clinic, the sooner we are going to come to a definite answer about this problem.

One problem was raised: the danger of using quinidine. Quinidine is certainly a dangerous drug. But against the danger of quinidine we are balancing the danger and the risk of the patient who suddenly develops postoperative atrial fibrillation. We cannot ignore the patients after lobectomy or pneumonectomy who have a normal sinus rhythm and develop atrial fibrillation. Most of us have seen some of these patients die because of the reduction in cardiac output that does occur as a result of this arrhythmia, so that if we can prevent atrial fibrillation I think means should be taken to do this.

(Slide) When quinidine is given it is quite important to appraise these patients daily, to watch their blood pressure several times each day and, most important, to monitor the electrocardiogram. There are definite changes that occur with quinidine dosage, and certainly these changes occur before we get to any fatal arrhythmia such as ventricular tachycardia or ventricular fibrillation.

These are the changes, briefly described here. Beginning with the normal electrocardiogram, first there is a terminal depression of S-T segment and a prolongation of the Q-T interval. This subsequently progresses to a widening of the QRS interval. Nausea, scotomata, or subjective symptoms are not considered an indication for decreasing or stopping quinidine.

Of all patients in whom quinidine was given, we have had only 1 patient who developed ventricular tachycardia. Fortunately this patient had no further serious difficulty. This developed in a rather unusual situation because this patient was receiving Banthine. We believe that because of the Banthine the absorption of quinidine was altered so that a higher blood level than usual developed.

I think we cannot ignore the factor of trauma to the left atrium as a cause for postoperative fibrillation because in the past month we have seen 2 patients with normal-sized left atria who had left atriotomies; 1 for the removal of a myxoma, another for an anastomosis of an anomalous left pulmonary vein. Both patients developed atrial fibrillation postoperatively. Neither had left atrial hypertension preoperatively.

RELATIVE ANTIHEPARIN POTENCY OF POLYBRENE AND PROTAMINE IN PATIENTS UNDERGOING EXTRACORPOREAL CIRCULATION

Arthur S. Keats, M.D., Denton A. Cooley, M.D., and Jane Telford, M.D., Houston, Texas

THE PRINCIPAL safety factor in the use of heparin to prevent coagulation of blood in several clinical situations has been the availability of an antagonist to treat overdosage or for prompt cessation of heparin effects when necessary. This antagonist, protamine sulfate, has been prompt, reliable, and predictable in its action. However, a number of undesirable side actions have followed its use, including dyspnea,[1] hypotension, bradycardia and, when given in excessive dose in vitro, an increase instead of decrease in coagulation time.[2]

In 1953, Preston and Parker[3] reported on the effectiveness of polybrene, a synthetic polymerized quaternary ammonium salt, as a heparin antagonist in vitro and in vivo, and estimated that 0.75 mg. of polybrene would neutralize 1.0 mg. of heparin. Weiss and his co-workers[4] reported the effective use of polybrene to neutralize heparin administered during extracorporeal circulation for open heart surgery. They also suggested that 0.7 mg. of polybrene was sufficient to antagonize the anticoagulant effect of 1 mg. of heparin. When administered to conscious patients, polybrene produced subjective effects described as a "colloid reaction," which included symptoms as dizziness, flushing of the face, dyspnea or wheezing, substernal pressure, lumbar pain, and weakness.

The present study was designed to determine the relative merits of protamine and polybrene as antagonists to heparin used during extracorporeal circulation. The proper comparison of drugs with similar primary actions requires that a precise estimate be made first of the relative potency of the drugs being compared.[5] Only then can relative side action liability be determined using equipotent doses. The failure to employ equipotent doses in studies of side action liability can lead to large errors in estimates of relative merits of drugs. This study was designed in this pattern.

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This study was supported in part by the C. J. Thibodeaux Foundation, Houston, Texas.
Received for publication March 9, 1959.

METHODS

Antiheparin Potency.—Forty noncyanotic patients undergoing extracorporeal circulation with a bubble oxygenator[6] for corrective open heart surgery were subjects for this assay. These patients included both children and adults and a variety of cardiac diseases (age range, 3 to 28 years; weight range, 22 to 136 pounds). Clotting times were determined by the Lee-White method, using 1.0 c.c. volume of blood in each of 3 tubes. The first tube was tilted every minute until a clot formed. Then the second tube was tilted similarly, then the third. The clotting time was the period between sampling of the blood and the time when the blood in all three tubes had clotted. All blood samples were collected from the right ventricle in dry 10 c.c. syringes with a 20 gauge needle. Samples were drawn at the following periods: (1) prior to heparinization, approximately 20 minutes before cardiopulmonary bypass; (2) 5 minutes after heparin administration; (3) 5 minutes after administration of the heparin antagonist, approximately 10 minutes after cardiopulmonary bypass; (4) 15 minutes after administration of the antagonist; and (5), in some patients, 5 minutes after administration of additional heparin antagonist.

The following doses of heparin antagonists were studied: protamine 1.5 mg., 2.0 mg., and 5.0 mg. per kilogram of body weight; polybrene 0.75 mg., 1.5 mg., and 3.0 mg. per kilogram of body weight. Prior to administration of either antagonist, 10 per cent calcium gluconate (0.5 to 1.0 Gm.) was administered intravenously to neutralize any citrate possibly circulating from banked blood administered prior to bypass. Both antagonists were injected in undiluted form over a period of 30 to 60 seconds. The usual time elapsing from the administration of heparin to administration of antagonist was 30 to 40 minutes.

In all patients, heparin (1.5 mg./Kg.) prolonged coagulation time by more than 60 minutes beyond the control (pre-heparin) clotting time. Assuming a 100 per cent heparin effect to be 60 minutes beyond control clotting time, the following formula was devised to express antiheparin potency following administration of an antagonist:

$$\%\ \text{heparin neutralization} = \frac{(\text{control clotting time} + 60) - \text{observed clotting time}}{60}.$$

Side Action Liability.—Eleven adult patients recovering from minor surgical procedures done under local or spinal anesthesia (without vasopressor) were subjects of this study. Undiluted protamine (5 mg./Kg.) or polybrene (3 mg./Kg.) was injected rapidly intravenously over a period of 30 to 60 seconds. Immediately before and after injection, blood pressure, pulse rate, and respiratory rate were recorded every minute for 5 minutes, then every 5 minutes for 20 minutes. Changes in pulse rate of less than 10 per minute, or of systolic or diastolic pressure of less than 10 mm. Hg, were not considered significant. The subjective effects produced by the drug were elicited by responses to nonspecific questions as "How do you feel?"

RESULTS

Relative Potency.—When the degree of heparin neutralization by both protamine and polybrene was compared at 5 and 15 minutes after administration (Table I), it was apparent that maximum antiheparin effect occurred with both drugs within 5 minutes. Therefore, clotting times 5 minutes after administration were used to determine relative potency. The 5-minute post-neutralization data as collected are presented in Table II. Except for the group which received 1.5 mg./Kg. of protamine, the duration of cardiopulmonary bypass was comparable in all groups as was the control clotting times in groups being compared. Per cent heparin neutralization was calculated for each individual and the means in Table II represent the means of individual values.

TABLE I. COMPARISON OF DEGREE OF HEPARIN NEUTRALIZATION AT 5 AND 15 MINUTES AFTER INTRAVENOUS ADMINISTRATION OF PROTAMINE AND POLYBRENE

DOSE (MG./KG.)	NUMBER OF PATIENTS	MEAN % HEPARIN NEUTRALIZATION	
		5 MIN. AFTER ADMINISTRATION	15 MIN. AFTER ADMINISTRATION
		Protamine	
1.5	3	21.7	26.7
2.0	2	71.5	50.0
5.0	5	98.4	98.4
		Polybrene	
0.75	5	24.2	15.0
1.5	5	96.0	92.0
3.0	7	100.7	97.3

TABLE II. EFFECTIVENESS OF THREE DOSE LEVELS OF PROTAMINE AND POLYBRENE IN NEUTRALIZING THE ANTICOAGULANT EFFECTS OF 1.5 MG./KG. OF HEPARIN

DOSE (MG./KG.)	NUMBER OF PATIENTS	DURATION OF BYPASS MIN. ± S.E.†	CONTROL CLOTTING TIME MIN. ± S.E.†	CLOTTING TIME 5 MIN. AFTER ANTAGONIST MIN. ± S.E.†	% HEPARIN NEUTRALIZATION* ± S.E.†
			Protamine		
1.5	5	7.8 ± 0.7	14.4 ± 2.6	54.6 ± 7.8	21.6 ± 13
2.0	6	12.4 ± 2.5	15.2 ± 3.1	31.7 ± 6.8	72.3 ± 11
5.0	5	14.4 ± 2.6	9.2 ± 0.5	10.2 ± 1.0	98.4 ± 2.3
			Polybrene		
0.75	5	14.4 ± 2.8	15.6 ± 3.7	61.0 ± 9.8	24.2 ± 15
1.5	11	13.5 ± 1.9	14.5 ± 1.7	16.5 ± 2.7	96.6 ± 3.1
3.0	8	16.9 ± 2.6	9.6 ± 0.4	9.5 ± 0.3	100.3 ± 0.9

*See text for definition.
†Standard error of mean.

These data were plotted as a dose effect relationship for each drug (Fig. 1), utilizing only the data of the two lower dose levels from each drug. The regression equation for each curve was calculated from a plot of individual values. The slopes of the two curves were strikingly similar and significant (polybrene: slope 96.6, $P < 0.01$; protamine: slope 101.7, $P < 0.02$). Covariance analysis of this block of data[7] indicated no significant difference between regression ($P > 0.05$) but a highly significant difference between curve means ($P < 0.01$). Because of the similar regression coefficients, curves

were not adjusted to a common slope and relative potency was estimated by calculation at 100 per cent heparin neutralization. This estimate was 1.54 mg./Kg. of polybrene or 2.27 mg./Kg. of protamine neutralized 1.5 mg./Kg. of heparin in this clinical situation. Expressed differently, polybrene was 1.5 times as potent as protamine at 100 per cent neutralization effect.

Additional data to support this estimate were obtained by the administration of additional doses of polybrene to patients whose clotting times did not return to control values after the initial dose of antagonist. In 4 patients, polybrene (1.5 mg./Kg.) given after protamine (1.5 mg./Kg.) increased heparin neutralization from 27 to 99 per cent. In 3 patients, polybrene (1.5 mg./Kg.) given after protamine (2.0 mg./Kg.) increased neutralization from 63 to 102 per cent. In 5 patients, polybrene (0.75 mg./Kg.) given after polybrene (0.75 mg./Kg.) increased heparin neutralization from 24 to 65 per cent. In 2 patients, who received polybrene (1.5 mg./Kg.), an additional dose of polybrene (1.5 mg./Kg.) did not significantly increase the degree of neutralization.

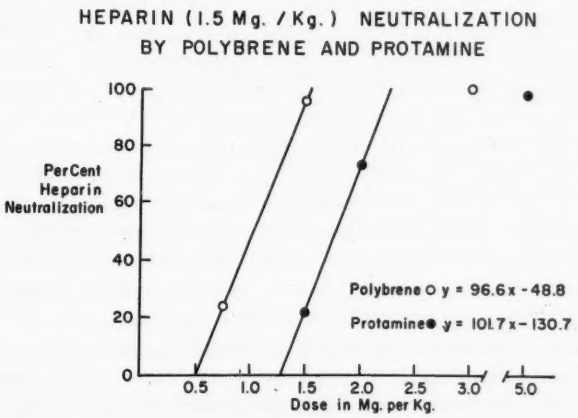

Fig. 1.—Relative antiheparin potency of polybrene and protamine expressed as a dose effect relationship. At 100 per cent heparin neutralization, 1.54 mg. per kilogram of polybrene is equivalent to 2.27 mg. per kilogram of protamine. At twice the neutralization dose, neither drug produces an anticoagulant effect.

Since excessive doses of protamine and polybrene have been reported to produce a heparin-like effect and prolong coagulation times,[2, 8] the effects of twice the estimated neutralizing dose was also studied. Five patients received 5 mg./Kg. of protamine and 8 patients, 3 mg./Kg. polybrene (Table II). Obviously, no anticoagulant effect was produced by these doses.

When used for cardiopulmonary bypass, the pump-oxygenator itself can induce clotting defects from trauma to the blood with consequent loss of fibrin and thrombocytes. It was, therefore, important to correlate the duration of perfusion with the degree of failure of heparin neutralization. This was done with the data of 16 patients in whom heparin effects were not completely antagonized by either antagonist. The correlation coefficient of the relationship between per cent heparin neutralization (range 0 to 75 per cent) and duration

of perfusion (range 5.0 to 22.5 min.) was 0.098. This indicated that no correlation existed and that other clotting defects which may have been produced by the pump-oxygenator probably did not account for the failure of clotting after administration of low doses of heparin antagonists.

The heparinized blood used in the pump-oxygenator contained 18 mg. of heparin per 500 c.c. It was therefore possible that the actual amount of heparin being neutralized in this study was more nearly 2.0 mg./Kg. than 1.5 mg./Kg. Assuming a 70 kilogram man has 5 liters of blood, the dose of 18 mg. of heparin per 500 c.c. of blood approximates an in vivo dose of 2.5 mg./Kg. The actual effective circulating heparin at the end of perfusion could therefore range between 1.5 and 2.5 mg./Kg. The exact amount would depend on the blood volume of the patient, the blood volume of the extracorporeal circuit, and the loss of heparin during blood storage.

Side Action Liability.—In the 40 patients used for the potency assay, both protamine and polybrene were injected intravenously undiluted over a period of 15 to 60 seconds. The injection was timed to follow immediately upon the removal of the cannulae from the venae cavae, if the pulse rate and blood pressure were stable and satisfactory. Marked hypotension did not occur in any patient following the rapid administration of either drug at any dose level. In some patients, decreases in systolic blood pressure of 10 to 20 mm.Hg were observed at some time during the 10-minute period which followed the administration of an antagonist. However, these pressure changes could be as readily attributed to the continuing blood loss from the cardiotomy incision as to the injection of the drug, since these events were simultaneous. When hypotension occurred, it was treated by transfusion. No patient received a vasopressor following cardiopulmonary bypass and no electrocardiographic changes could be attributed to the injection of these drugs.

The data obtained from the 11 postoperative patients given protamine and polybrene are summarized in Table III. Large doses (twice the neutralizing dose) and rapid injections were used to magnify any changes which might occur. It is obvious that both drugs did surprisingly little. Protamine tended to have a greater hypotensive effect than polybrene. The blood pressure of one patient given protamine decreased from 120/70 to 90/60 mm. Hg and remained low for 20 minutes when a vasopressor was given. No alarming effects appeared in any patient. Most changes, including all symptoms, lasted less than 5 minutes and occurred primarily during 1 or 2 minutes after rapid injection.

DISCUSSION

When given in equipotent doses, both protamine and polybrene are effective heparin antagonists. After intravenous administration, both drugs exert their maximum effect within 5 minutes. Heparin neutralization by either drug was sustained, since no patient required additional amounts of protamine or polybrene in the postoperative period and clotting times, done one hour postoperatively, were in the normal range. From this study a precise statement

TABLE III. SIDE ACTION LIABILITY OF INTRAVENOUS PROTAMINE AND POLYBRENE IN CONSCIOUS SUBJECTS

	DRUG	
	PROTAMINE (5 MG./KG.)	POLYBRENE (3 MG./KG.)
Subjects	6 (ages 16-57)	5 (ages 21-62)
Total Dose mg. c.c.	 270-450 mg. 27-45 c.c.	 180-230 mg. 18- 23 c.c.
Blood pressure change	Decreased in 6 Mean decrease: 19 mm. systolic 9 mm. diastolic Duration—5 min. in 4 Duration—5 to 20 min. in 2	Decreased in 1 140/70 to 120/70 for 2 min. No change in 4
Pulse rate change	No change in 2 Increased (25/min.) in 4 Duration—5 to 10 min. in 4	Decreased (12/min.) in 2 Increased (25/min.) in 3 Duration—5 min. in 5
Respiration	No change in 6	No change in 4 Hyperventilation in 1
Symptoms (no. of subjects)	Bad taste—1 Flushed face—2 Arm pain—1 Stinging all over—1 No effect—3	Bad taste—3 Substernal discomfort—1 Restlessness—1 Generalized muscle spasm—1 No effect—1

as to the dose of protamine or polybrene required to neutralize 1.0 mg. of heparin cannot be made since the exact amount of effective circulating heparin at the end of extracorporeal circulation could not be determined. However, a precise estimate of the relative antiheparin potency of protamine and polybrene can be made, namely, polybrene is 1.5 times as potent as protamine at 100 per cent antiheparin effect.

In both anesthetized and awake patients, protamine and polybrene are remarkably free from serious side actions. Even with rapid intravenous injection, at twice the neutralizing dose, in patients who had undergone extracorporeal circulation, no marked hypotension resulted. In conscious subjects, protamine tended to produce more hypotension than polybrene, but the hypotension was not severe in any patient. The subjective effects produced by both drugs were unpleasant, but mild and transient. Except for hyperventilation in one instance after polybrene, no dyspnea, wheezing, bronchospasm, or allergic phenomena were observed in these patients. There was no evidence of an anticoagulant effect from large doses of protamine or polybrene. Both drugs have a wide margin of safety.

Heparin is administered intravenously to our patients at 1.5 mg. per kilogram of body weight just before cannulation for bypass. In order to antagonize heparin we currently administer 2.5 mg. to 3 mg. per kilogram of polybrene rapidly intravenously upon the removal of the cannulae from the venae cavae. This has proved satisfactory and safe. Our preference for polybrene is based primarily on ease of administration and, secondarily, on a lesser hypotensive effect. Polybrene is packaged in a 10 c.c. ampule containing 100 mg., whereas protamine is contained in a 5 c.c. ampule at the same

concentration. Therefore, fewer ampules of polybrene are required for the adult patient and a smaller volume can be injected because of increased potency. In addition, polybrene solution shows no tendency to foam as does protamine. When blood replacement has been adequate, hypotension following protamine has not been a problem in our experience.[9] Others, however, have been troubled by "protamine shock."[2] We have chosen a polybrene dose greater than 1.5 mg./Kg. because of its safety and in order to ensure complete heparin neutralization since it is possible that circulating heparin after extracorporeal circulation may be as high as 2.5 mg./Kg.

SUMMARY

In 40 patients undergoing extracorporeal circulation, the relative antiheparin potency of 3 dose levels of polybrene and 3 dose levels of protamine have been determined by Lee-White clotting times after administration of 1.5 mg./Kg. of heparin. At 100 per cent heparin neutralization, polybrene was 1.5 times as potent as protamine. Heparin neutralization by both drugs after rapid intravenous administration was maximum within 5 minutes and was sustained. The side actions produced by these drugs were noted in anesthetized patients and in 11 conscious adults. Protamine tended to produce mild hypotension in conscious subjects whereas polybrene produced no such response. Subjective effects produced by both drugs at twice the heparin neutralization dose were mild and transient.

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COARCTATION OF THE AORTA WITH PROXIMAL AORTIC DILATATION AND CALCIFIC ATHEROMATOUS DEGENERATION CORRECTED BY ENDARTERECTOMY

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DILATATION and degenerative changes of the aorta lying proximal to a coarctation are frequent findings in the surgical repair of this congenital anomaly. In a study of 200 collected cases of adult coarctation, Abbott[1] described proximal aortic dilatation and atheromatous degeneration to a greater or lesser extent in 50 per cent of the cases. When these changes in the aortic wall are pronounced, the difficulties of operative correction and the incidence of postoperative hemorrhage are appreciably increased. The accepted procedure of resection and anastomosis in such cases presents a formidable surgical problem, generally accompanied by a high operative mortality. In the case reported herein, a successful correction of a coarctation associated with severe dilatation and calcific atheromatous changes in the proximal aorta was accomplished by employing a modification of the technique of endarterectomy. This case is presented as a successful example of the use of an alternate method in the treatment of this particular surgical problem.

CASE REPORT

The patient was a 27-year-old white married woman who was referred to the University of California Medical Center, Los Angeles, in Oct. 1957, for evaluation of a known hypertension of 7 years' duration. Hypertension was first diagnosed in 1950 by her family physician when a blood pressure of 190/80 mm. Hg was recorded during a routine physical examination. A thorough work-up in 1951 at a metropolitan New York hospital revealed that the patient had always been asymptomatic, active physically, and had progressed normally through two pregnancies. Further work-up at that time revealed a blood pressure of 165/65 mm. Hg in the right arm and 108/70 mm. Hg in the right leg. She was a well-developed, well-nourished woman with the only positive findings limited to her cardiovascular system. She had bilateral bounding carotid pulses and a Grade 2 systolic murmur audible over the entire precordium. The heart was not enlarged. Femoral pulsations were markedly diminished bilaterally. An electrocardiogram showed a vertical electrical axis with a normal sinus rhythm. Roentgenogram of the chest demonstrated advanced calcific sclerosis and dilatation of the ascending aorta and the aortic arch and its branches, terminating several centimeters distal to the left subclavian artery. No

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This work was supported by U.S. Public Health Service Grant-in-aid No. H-1787.
Received for publication March 12, 1959.

notching of the ribs was visible. An angiocardiogram of the right side of the heart was normal. An aortogram, however, revealed a markedly dilated, proximal aorta, 40 mm. in diameter, which narrowed to 17 mm. in diameter in the descending aorta. The impression recorded in 1951 was that the patient had hypertension of the upper extremities with marked atherosclerosis of the proximal aorta and probable coarctation. Since 1951, the patient had been on antihypertensive drugs and had remained well except for increasing fatigability and mild exertional dyspnea.

On admission to this institution in 1957, the patient's blood pressure in each arm was 240/70 mm. Hg and in each lower extremity was 110/75 mm. Hg. The femoral pulsations were barely palpable. A blowing, Grade 4 systolic murmur was heard over the

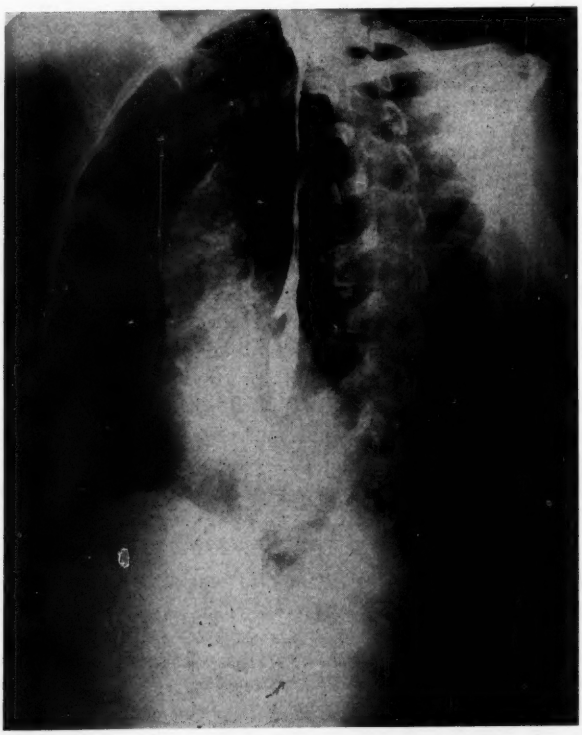

Fig. 1.—Left anterior oblique chest x-ray demonstrating marked dilatation and calcification of proximal aorta and aortic arch branches.

precordium, which transmitted into the neck and axilla. A Grade 2 early diastolic murmur was audible along the left sternal border in the fourth interspace. An electrocardiogram revealed left ventricular hypertrophy. A moderate cardiomegaly was present on roentgenogram, and the previous severe calcific atherosclerosis of the proximal aorta associated with diffuse dilatation and prompt narrowing of the aorta, distal to the left subclavian artery, was again visualized (Fig. 1). Intravenous pyelograms and renal chemistries were normal. Serological tests for syphilis were negative. The preoperative diagnosis was coarctation of the aorta with extensive proximal calcific sclerosis and dilatation, cardiomegaly, and aortic insufficiency.

On Jan. 10, 1958, a left posterolateral thoracotomy was made through the bed of the fifth rib, and the fourth and sixth ribs were divided posteriorly. A very dilated calcific

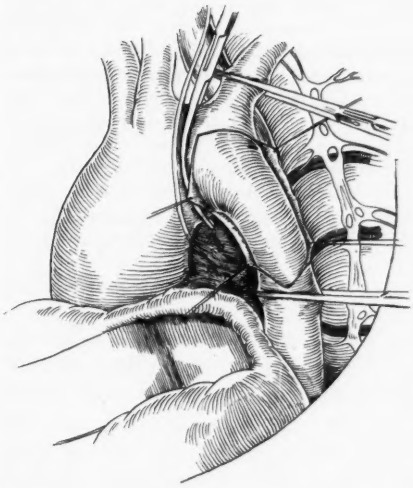

Fig. 2.

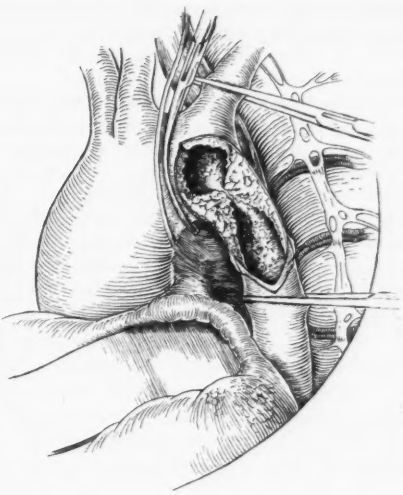

Fig. 3.

Fig. 2.—Left posterolateral thoracotomy. The visceral pleura is incised over the coarctation segment. The discrepancy in vessel diameter in the proximal and distal aorta is demonstrated.

Fig. 3.—Aortotomy over the coarctation revealing heavy calcific atheromatous plaque deposition in the proximal aorta and stenotic area with almost total obstruction of the aortic lumen.

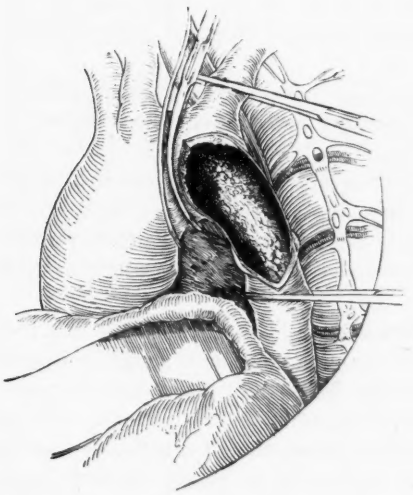

Fig. 4.

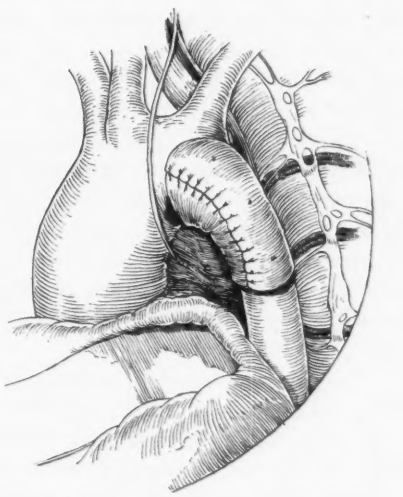

Fig. 5.

Fig. 4.—Aortic lumen restored to an adequate diameter following endarterectomy of obstructing process.

Fig. 5.—Aortic homograft sutured over thinned-out wall and aortotomy.

aorta extended from the aortic valve to 1 cm. distal to the left subclavian artery; at this point, the aorta narrowed to one third its proximal diameter with a faint pulsation distally (Fig. 2). The strictured area did not resemble a typical coarctation, since its external diameter was only slightly less than a normal-sized descending aorta. The intercostal arteries were moderately dilated. After the left subclavian artery and proximal and distal aorta were controlled, a longitudinal aortotomy was made through the area of coarctation. The lumen was almost totally obstructed with atheromatous deposits which lined the stenosed segment of aorta (Fig. 3). The obstructing calcific deposits were freed from the aortic wall by sharp and blunt dissection to a point just proximal to the left subclavian artery. A lumen of 1.5 to 2.0 cm. was obtained through the stenosed area (Fig. 4). The aortotomy was closed with a continuous 3-0 silk suture and reinforced with an aortic homograft, since the aortic wall was extremely thin in the endarterectomized segment (Fig. 5). During the occlusion of the proximal aorta, Arfonad maintained the blood pressure in the upper extremities below 200 mm. Hg.

The patient tolerated the operative procedure quite well, and her postoperative course was uncomplicated. Simultaneous brachial and femoral artery pressure of 250/78 and 215/80 mm. Hg, respectively, were recorded postoperatively. The patient is now one year postoperative and blood pressures taken at this time are 158/54 mm. Hg in the right arm and 180/100 mm. Hg in the right leg. The patient leads a normal life at the present time and has begun lessons in water skiing.

DISCUSSION

The dilatation and degenerative changes observed in the aorta proximal to a coarctation are generally believed to result from stresses of increased intraluminal pressure. Clagett[2] felt that the degree of vascular damage in the proximal aorta is related directly to the duration of the lesion. He found that the patients with coarctation with extensive vascular damage had an average age older than those with minimal or moderate damage. He also postulated that the degree of vascular damage was related to the amount of physical exertion and resultant strain on the cardiovascular system, since the more extensive changes were present predominantly in males.

Another possible factor in the etiology of these changes in the vessel wall is an inherent weakness in the media of the aortic wall itself. It is difficult to determine whether the elastic fiber deficiency and fibrous replacement described in the proximal aorta in young adults with coarctation is congenital in origin or secondary to stress.[3-5] It would be necessary to study the aorta in infants and children with coarctation, presumably before intraluminal pressure would have had any effect, in order to postulate a congenital weakness underlying these changes in the vessel wall.

In the case reported, severe dilatation and calcification of the proximal aorta prohibited the usual procedure of resection and anastomosis. Since the circumference of the strictured segment was only slightly less than normal, it was felt that the obstructive process could be removed intraluminally through a longitudinal aortotomy. The progressive accumulation of calcified deposits on a previously congenitally stenotic area resulted in an almost complete aortic obstruction. We feel that this patient never had a typical coarctation, but rather a congenital narrowing of the aorta distal to the left subclavian artery

which was probably compatible with normal life expectancy until she acquired pronounced secondary changes in the proximal vessel wall and coarctation segment itself.

Thromboendarterectomy has been employed more extensively in recent years in the attack on occlusive arterial disease. Favorable experience has accumulated using this technique in arteriosclerotic occlusive disease of the aortic, iliac, femoral, renal, carotid, and coronary arteries. The usual type of coarctation, with its pronounced narrowing of the entire diameter of the aortic wall, is only correctible by resection. However, in situations where the size of the coarctation segment is larger and the changes in the vessel wall are pronounced, endarterectomy may be employed successfully with less risk to the patient.

SUMMARY

The successful correction of a coarctation of the aorta, associated with severe dilatation and atheromatous degeneration of the proximal vessel wall, remains a hazardous surgical problem. In the case reported, the proximal aorta as well as the coarctation segment were involved with calcific atheromatous degeneration. The constricted segment was restored to an adequate lumen by a longitudinal aortotomy and endarterectomy. This operative approach, although not applicable in the majority of cases of coarctation, is recommended as an alternate procedure in selected patients.

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TREATMENT AND PALLIATION OF CARCINOMA OF THE ESOPHAGUS BY TWO-STAGE ESOPHAGECTOMY AND ESOPHAGOCOLOGASTROSTOMY

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CARCINOMA of the esophagus, in most cases, is a fatal tumor; it is difficult to palliate, and is a challenge to all interested in the disease.

Watson and associates[1] reviewed 993 cases seen at Memorial Center in New York and found only a 2 per cent over-all 5 year survival rate. The cause for low salvage rate for patients with this disease is due to several reasons. Many times it is due to failure of the patient to consult his physician at the onset of trouble. In other instances, it is due to the physician's failure to study thoroughly and diagnose the case. A vital factor, however, is the problem of insufficient resection which results in incomplete removal of the esophagus and its metastatic extensions. Scanlon, Morton, Walker, and Watson[2] have pointed out that carcinoma of the esophagus frequently extends through the submucosal lymphatics, beyond the gross limits of tumor, and in a group of 79 patients who had esophagectomy, 45.6 per cent had inadequate removal of the esophagus because tumor was present in the edge of the specimen or in submucosal lymphatics in that area.

The only answer to the above deficiency lies in total esophagectomy similar to the Torek procedure. By utilizing this principle, and using the colon to replace the esophagus as an esophagocologastrostomy, one can do a more thorough operation for cancer. It also provides excellent palliation for incurable cases and, if done in two stages, the procedure is clinically safe.

We have utilized the above-mentioned principle in 13 cases of carcinoma of the esophagus or upper stomach. In 5 of the 13 cases, at the time of thoracotomy, the lesion was found to be nonresectable so esophagocologastrostomy was done as a palliative procedure. Two deaths resulted after attempts to do esophagocologastrostomy and esophagectomy as one-stage procedures. These deaths precipitated our decision to adopt the two-stage operation because usually the poor condition of the patient will not permit the entire procedure to be done

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Received for publication Feb. 24, 1959.

at one time with reasonable safety. Esophagocologastrostomy and resection in two stages have been completed in 3 patients. A brief summary of our total experience follows.

REPORT OF CASES

CASE 1.—(JGH-278877.) C. F., a woman 56 years of age, was admitted on July 31, 1956, because of dysphagia. Roentgenograms disclosed an obstructing lesion in the mid-esophagus, and the specimen taken for biopsy through the esophagoscope showed squamous-cell carcinoma. Esophagocologastrostomy and resection of the entire esophagus was done in one stage, utilizing two surgical teams. Regardless of treatment, the patient went into shock and died on the second day following surgical intervention.

Permission was not given for necropsy.

CASE 2.—(BMH-235636.) P. B., a 59-year-old woman, was admitted on Dec. 7, 1956, with a complaint of dysphagia. An epidermoid carcinoma of the esophagus had been diagnosed in 1955; roentgen therapy had been given and gastrostomy done. She apparently responded well to roentgen therapy but could not swallow. On Dec. 21, 1956, an esophagocologastrostomy was done; the colon was brought into the neck through a retrosternal tunnel. The patient recovered and was able to take a regular diet for 2 years. She died 26 months after surgery.

CASE 3.—(BMH-238220.) R. B., a man 42 years of age, was admitted on Jan. 8, 1957, complaining of throat pain of 2 months' duration. Roentgen study revealed a tumor in the distal esophagus. This was confirmed by esophagoscopy, and biopsy showed the tumor was an adenocarcinoma.

Surgical exploration revealed an extensive tumor involving the lower esophagus and upper stomach. Esophagogastrectomy and esophagocologastrostomy were done with the colon brought through the esophageal hiatus, and the esophagocolic anastomosis was made high within the thorax.

The patient recovered from the operation, but he had a difficult postoperative course which was marked by development of localized empyema. This patient died 10 months later, but during that period he had no difficulty eating his food.

CASE 4.—(BMH-257618.) J. T., a 78-year-old woman, was admitted July 15, 1957, with a history of progressive dysphagia of 6 weeks' duration. The patient was found to have carcinoma of the cardia involving the lower esophagus. At surgical exploration, the lesion was found to be nonresectable so an esophagocologastrostomy was done with the colon brought into a retrosternal position.

The patient died of cardiac complications on the ninth day following the operation.

CASE 5.—(JGH-295983.) N. W., a woman 49 years of age, was admitted on Aug. 12, 1957, complaining of progressive dysphagia. Studies revealed a squamous-cell carcinoma of the upper and middle esophagus.

A one-stage total esophagectomy and esophagocologastrostomy were carried out with the colon brought into the neck through a retrosternal tunnel. The patient seemed to tolerate the procedure well but suddenly went into progressive shock and died on the second postoperative day.

Permission for necropsy was refused.

CASE 6.—(JGH-296007.) T. M., a man 58 years of age, was admitted on Aug. 26, 1957, complaining of dysphagia of one month's duration. Studies confirmed a diagnosis of squamous-cell carcinoma of the upper esophagus.

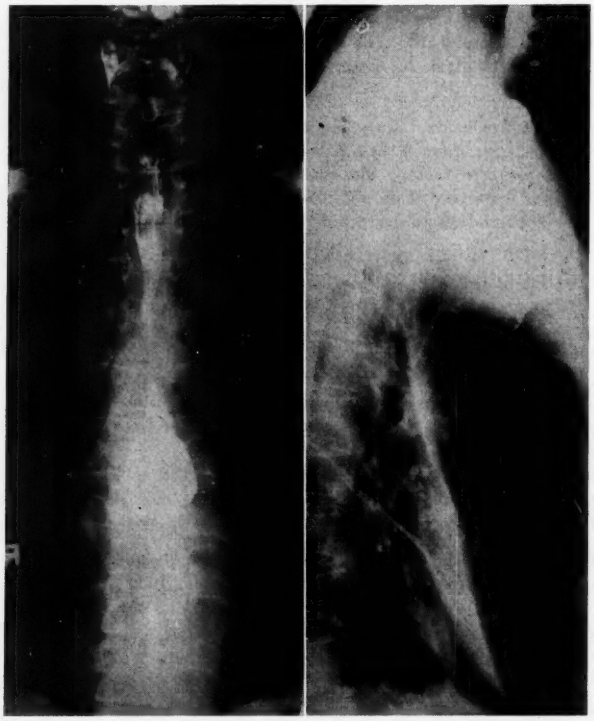
This patient was operated on in two stages. At the first stage, an esophagocologastrostomy was done with the colon brought into the neck retrosternally. The patient had some temporary anorexia but was taking a soft diet by the twelfth postoperative day.

One month after the first stage operation, a total esophagectomy was done. He was dismissed in good condition on the eighth day and was taking a regular diet.

Cobalt teletherapy was given postoperatively.

The patient died 7 months later. He was able to eat without difficulty, but during the last month of his life he developed anorexia.

CASE 7.—(JGH-132966.) E. S., a 49-year-old man, was admitted on Aug. 8, 1957, with a chief complaint of progressive dysphagia. Studies revealed that he had a squamous-cell carcinoma of the middle esophagus.



A. *B.*

Fig. 1.—Case 9. *A*, Preoperative esophagogram showing constrictive lesion at the junction of the middle and lower thirds of the esophagus.
B, Postoperative view of the substernal colon. Emptying was so rapid the picture resembles an air contrast enema.

As a first stage surgical operation, an esophagocologastrostomy was done, and the colon was brought into the neck through a retrosternal tunnel. Two weeks after this procedure, a total esophagectomy and repair of an inguinal hernia were done. When the patient was discharged 9 days later he was able to eat a regular diet.

He received cobalt teletherapy later and, when last seen 7 months after his hospital dismissal, he was doing well and had gained fourteen pounds.

CASE 8.—(JGH-92928.) W. B., a 57-year-old man, was admitted in August, 1957, complaining of cough on deglutition. He was found to have carcinoma of the esophagus

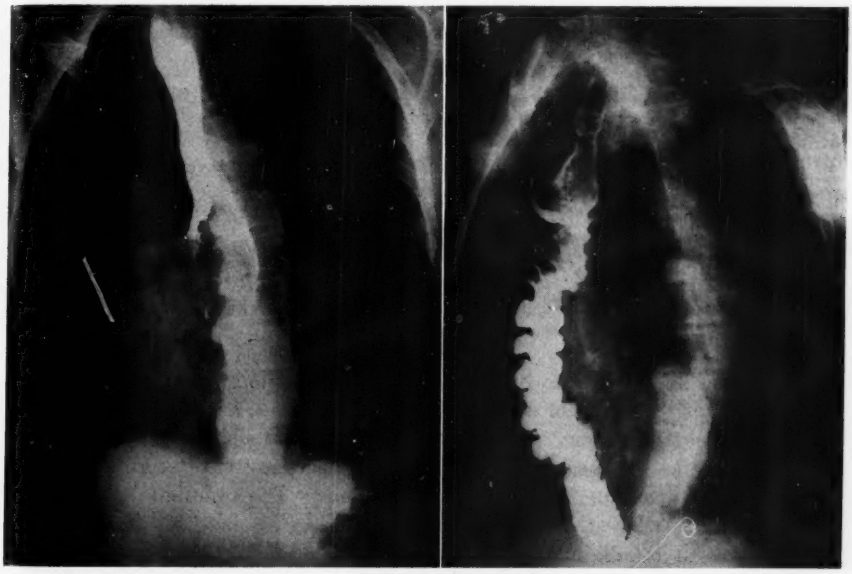
with a malignant tracheoesophageal fistula. A Levin tube was placed into the stomach and the patient was dismissed.

He was readmitted on Sept. 29, 1957, and a palliative esophagocologastrostomy was done. He did well for one week and was eating a regular diet when a fistula developed at the esophagocolic anastomosis. An unsuccessful attempt was made to close this fistula so a gastrostomy was done. He was last observed in January, 1958, and was doing poorly.

CASE 9.—(BMH-275132.) H. G., a man aged 59, was admitted with a complaint of dysphagia of 3 months' duration. Studies revealed a carcinoma of the middle esophagus (Fig. 1, *A*).

An esophagocologastrostomy was done as a first stage operation (Fig. 1, *B*) and his recovery was uneventful except for a small fistula in the neck which closed in 3 days. The patient was able to eat well and insisted on returning home 3 weeks after surgery.

He returned one month later; a thoracotomy was done, but his lesion was nonresectable. Cobalt therapy was given. The patient died 10 months later, but he was able to eat until the time of his death.



A. *B.*

Fig. 2.—Case 12. *A*, Esophagogram showing a large lesion in the middle third of the esophagus.

B, Postoperative esophagocologram showing free passage of barium through the anastomosis and colon.

CASE 10.—(BMH-271106.) W. S., a man 66 years of age, was admitted on Nov. 18, 1957, complaining of dysphagia of 4 months' duration. Studies revealed a squamous-cell carcinoma in the upper esophagus.

The patient had an esophagocologastrostomy performed on Nov. 25, 1957, when the colon was brought up into the neck through a retrosternal tunnel.

A subsequent separation of the abdominal wound was resutured on Dec. 5, 1957.

On Dec. 18, 1957, a thoracotomy proved the lesion was nonresectable. The patient was discharged on a soft diet and was eating well. The patient was still living at follow-up in November, 1958.

CASE 11.—(JGH-307878.) E. W., a woman 52 years of age, was admitted with a chief complaint of dysphagia of one month's duration. She was found to have a squamous-cell carcinoma of the middle esophagus. This patient was also found to have bilateral arteriosclerotic obstruction of the carotid arteries.

Bilateral carotid endarterectomy was done first, and one month later an esophagocologastrostomy was done. The patient died 3 weeks later. The necropsy revealed multiple cerebral infarcts to be the cause of death.

CASE 12.—(JGH-254278.) W. K., a man 67 years of age, was admitted on Jan. 3, 1958, with a complaint of dysphagia of 2 months' duration. Studies revealed a squamous-cell carcinoma of the middle esophagus (Fig. 2, *A*).

On Jan. 16, 1958, he had an esophagocologastrostomy (Fig. 2, *B*) and this was followed by a total esophagectomy on Feb. 6, 1958. He recovered from these procedures and was dismissed from the hospital on Feb. 29, 1958.

He was readmitted on June 27, 1958, with a complaint of nausea and vomiting, and roentgenogram showed gastric retention. A gastroenterostomy was done and he recovered satisfactorily.

He was last seen on Aug. 1, 1958, at which time he was eating a regular diet and had gained three pounds.

CASE 13.—(BMH-286387.) S. W., a man aged 65, was admitted on April 13, 1958, with a complaint of dysphagia which he had had for 3 months. Studies revealed an adenocarcinoma of the esophagogastric junction.

On April 23, 1958, an esophagocologastrostomy, along with a pyloroplasty and gastrostomy, were performed. When he had a thoracotomy 2 weeks after those procedures, the esophagogastric junction was resected but a tracheotomy was necessary in the immediate period following operation because of excessive tracheal secretions. The patient recovered and was dismissed on June 15, 1958, at which time he was taking a soft diet. He died 7 months later of carcinomatosis.

TECHNIQUE

We have abandoned the one-stage total esophagectomy and esophagocologastrostomy for treatment of carcinoma of the esophagus, and now prefer to do an esophagocologastrostomy as the first stage surgical operation and a total esophagectomy as the second stage. The esophagectomy can usually be done within 2 weeks after the first stage has been done. The technique of the first stage procedure follows.

The patient is admitted to the hospital a few days before he is to have operation, and the colon is cleansed by enemas and purgatives; it is sterilized by Neomycin and one of the nonabsorbable sulfa drugs.

At operation, the patient is placed in the supine position, and a long, midline incision is made. The right colon is mobilized and an appendectomy is done. The ileocolic and right colic vessels are divided, care being taken to preserve the marginal vessels and middle colic vessels. The colon is divided in its transverse portion to the left of the midline, and the ileum is divided at the ileocecal junction and the distal ileum is closed by inversion. This is followed by an ileotransverse colostomy, and when this anastomosis is begun, a second team of surgeons begins its procedure in the neck.

An incision is made along the inner margin of the sternomastoid muscle on the left side; the cervical esophagus is mobilized and divided just above the thoracic inlet, and the distal portion is inverted, closed, and allowed to drop

back into the mediastinum. A retrosternal tunnel is then developed by blunt dissection with the fingers, care being taken so the pleura will not be torn. On occasion we have resected the medial end of the clavicle to enlarge the thoracic inlet. The retrosternal tunnel is developed simultaneously from the abdominal end by another team of surgeons until a space is obtained from neck to abdomen which will admit the colon without tension or compression. The colon, cecum first, is then passed behind the stomach, into the tunnel, and into the neck. It is usually necessary to both gently push and pull the colon through the tunnel, and a long thread in the cecal end is pulled from above, thus assisting the passage of the bowel. The cecum is then anastomosed to the esophagus using interrupted silk sutures in two layers, and the anastomosis of the distal colon into the anterior wall of the stomach is placed as high as is technically feasible. A pyloroplasty or pyloromyotomy is then done. A Levin tube may be passed through the colon, but since this is fairly difficult to accomplish, we usually have eliminated a tube completely or inserted one through a gastrostomy.

The patient is allowed to have surgical liquids on the third or fourth day following operation and, if his progress is satisfactory, he is given a soft diet in one week.

The second stage of the operative procedure involves resection of the entire esophagus from the previously closed cervicomediastinal portion down to the esophagogastric junction. This is through a right thoracotomy incision in the fifth or sixth interspace depending upon the level of the lesion. The esophagectomy is usually quite easy, atraumatic for the patient, and can be done in an hour or less. The patient usually can be dismissed about 6 to 8 days after this stage.

MORTALITY AND COMPLICATIONS

Two of our patients who had one-stage procedures developed shock after operation and died. This caused us to stage the procedure, and we have had no other patient develop this complication. One patient developed cardiac failure and died. Another patient who died had esophagocologastrostomy subsequent to bilateral carotid endarterectomies. Necropsy determined that this patient had multiple cerebral infarcts. We believe that in this case the complications properly should be ascribed to the previous carotid artery surgery.

Two patients each developed an esophageal fistula in the neck. One fistula closed promptly, but the other failed to close and resulted in failure of the operation.

Other complications encountered were localized empyema in one case, wound separation in one case, excess tracheal secretions necessitating tracheotomy in one case, and late pyloric obstruction in one case.

DISCUSSION

Numerous methods have been used to replace or substitute for the esophagus after esophagectomy, but all methods have had their limitations and undesirable

features. Until recently the most commonly used method of esophageal substitution was the use of the stomach which was mobilized and drawn up into the chest. The major disadvantage of this method was the resultant peptic esophagitis in about 60 per cent of the cases.

Regurgitation and anorexia are additional problems to cope with after esophagogastrostomy. The higher the lesion is located in the esophagus, the greater becomes the problem of inadequate blood supply, and the greater the risk of surgical mortality.

The use of jejunal loops is attended by high incidence of difficulties with blood supply and, if the anastomosis is in the thoracic cavity, the mortality is high.

The construction of skin tubes and similar procedures has never become popular because of the time, expense, and numerous operations necessary to carry a case to completion.

Kelling[3] and Vulliet,[4] in 1911, working independently, apparently were the first to utilize the colon as an esophageal substitute. Von Hacker,[5] in 1914, and Roith,[6] in 1923, reported cases in which the colon was used as a substitute for the esophagus.

Ochsner[7] reviewed the literature from 1911 to 1934 and found 20 cases of subcutaneous colon transplants. This type of operation did not become popular until improved colon sterilization became possible, but in the past 5 years, numerous cases have been reported in the literature. This procedure lends itself to cases of esophageal atresia, esophageal stricture, esophageal obstruction due to malignancy, and to cases requiring esophageal resection. The transplantation may be accomplished by employing the right and transverse colon, the transverse colon alone, or the left colon. The colon may be brought into the thorax via the esophageal hiatus, through a separate opening in the diaphragm, or through a retrosternal or subcutaneous tunnel. Advantages of using the colon in this manner follow.

1. The blood supply of the colon usually allows one to mobilize a sufficient length to reach the pharynx and still have adequate circulation to the distal end. This makes it superior to the jejunum as a replacement part because the blood supply of the jejunum is often not sufficient to allow one to mobilize a long segment.

2. The colon is apparently resistant to acid peptic digestion. Ivy,[8] Wangensteen,[9] and others have shown that the colon's resistance to gastric secretion is greater than that of the jejunum or the esophagus. In approximately 75 cases of esophagocologastrostomy which we have found reported in the literature, or have knowledge of, there has been only one in which marginal ulceration has occurred.[10] This is in contrast to cases in which the stomach is anastomosed to the esophagus and in which nearly 60 per cent develop acid peptic esophagitis.[11]

3. The use of the colon has another advantage in that the stomach remains in its normal location, performing its normal function as a reservoir, and not functioning as a transit tube. We believe this is the reason why the patient

who has had esophagocologastrostomy has fewer digestive disturbances and better nutrition than the patient who has had esophagogastrostomy. We have formulated our impression from experience gathered from 20 cases of esophagocologastrostomy which were done for various conditions.

With the use of the colon as replacement for the esophagus, in nearly all cases, one is able to bring the colon to the neck, and thus an anastomosis can be made in the neck instead of in the chest. If leakage should occur, only a small focal abscess and/or fistula develops in the neck. However, if anastomosis is made in the chest and leakage occurs, empyema and severe sepsis can result and this complication carries a high mortality rate. We feel that in most cases the colon should be brought through a retrosternal tunnel into the neck and anastomosis made there instead of in the intrapleural space.

The original Torek operation which removes the esophagus and leaves an esophageal fistula and gastrostomy is the more satisfactory operation for esophageal cancer than any since described because it provides for a wide resection of the esophagus. The disadvantage of esophageal fistula and gastrostomy now is corrected readily by esophagocologastrostomy. Scanlon, Morton, Walker, and Watson have recently advocated return to the Torek procedure, and we concur with them.

We have chosen to do the esophagocologastrostomy as the first stage procedure instead of first resecting the esophagus. We made this choice because we have observed that in most cases of carcinoma of the esophagus, the nutrition of the patient is very poor, and this best can be corrected by furnishing the patient a route for swallowing rather than by gastrostomy. Second, in many instances, esophagocologastrostomy is palliative, and we feel it would be difficult to convince patients that a second major operation must be done after finding a nonresectable lesion at thoracotomy as the first stage.

Theoretically, one first should remove the neoplasm and delay reconstruction until later; however, we feel that the 2 week delay between stages does not result in significant increased metastases or shortened patient survivals.

One of the disadvantages of treatment by roentgen therapy in the past has been the complication of stricture in the area of the neoplasm. We hope that creating a channel for deglutition in an area far removed from the lesion being treated will allow more intensive roentgen treatment for patients with nonresectable lesions. More intensive treatment should also be possible for those receiving treatment after resection. Only more experience and observation will teach us if this is an advantage.

RESULTS

The results in our series of 13 cases are listed in Table I.

Four patients died in the postoperative period. Two of these died of shock and, because of this experience, we have abandoned the use of the single stage esophagocologastrostomy and esophagectomy. One patient died of cardiac failure and one of cerebral infarction.

Although our mortality rate is high, blame, in part, can be laid to the fact that many of these patients are poor risks due to malnutrition, vitamin deficiency, and similar conditions. Also, one expects some higher degree of morbidity and mortality when performing a new type of procedure. We feel that staging the procedures and more operating experience will decrease our operative mortality and morbidity. This has been true in our more recent experience.

TABLE I

CASE	LOCATION OF LESION	PROCEDURE	RESULTS
1	Mid-esophagus	Esophagocologastrostomy and resection in one stage	Postoperative death
2	Upper esophagus	Esophagocologastrostomy and roentgen therapy	Lived 26 months
3	Low esophagus and stomach	Esophagocologastrostomy and resection in one stage	Lived 10 months
4	Low esophagus and stomach	Esophagocologastrostomy	Postoperative death
5	Upper esophagus	Esophagocologastrostomy and resection in one stage	Postoperative death
6	Upper esophagus	Esophagocologastrostomy and resection in two stages	Lived 7 months
7	Middle esophagus	Esophagocologastrostomy and resection in two stages	Alive and eating well
8	Middle esophagus with tracheoesophageal fistula	Esophagocologastrostomy	Unimproved due to cervical fistula
9	Middle esophagus	Esophagocologastrostomy and roentgen therapy; lesion nonresectable at thoracotomy	Lived 10 months
10	Upper esophagus	Esophagocologastrostomy; lesion nonresectable at second stage	Living 1 year later
11	Middle esophagus	Esophagocologastrostomy	Postoperative death (cerebral infarction)
12	Lower esophagus	Esophagocologastrostomy and resection in two stages	Alive and eating well 7 months postoperative
13	Lower esophagus and upper stomach	Esophagocologastrostomy and resection (palliative) in two stages	Lived 7 months

SUMMARY

1. Because of submucosal extension of carcinoma of the esophagus, many patients who have had subtotal esophagectomy have had inadequate resection.

2. The Torek procedure, combined with reconstruction, utilizing the right and transverse colon, in suitable cases, offers a better operation for cancer.

3. In nonresectable cases, esophagocologastrostomy results in the best palliation we have observed with reference to swallowing, weight gain, and freedom from undesirable side effects.

4. The use of the colon in esophagoplasty, we believe, is preferable to the use of the stomach or jejunum.

5. Eleven cases of carcinoma of the esophagus and 2 cases of carcinoma of the esophagogastric junction have been treated by esophagocologastrostomy combined with resection.

6. Four of the aforementioned patients died in the immediate period following surgical operation; 2 developed esophagocutaneous fistulas, one of which closed in 3 days. Other complications were reversible and were corrected.

7. The patients who survived the operative procedures obtained excellent palliation, and we believe that the patients who have had resection have a better chance for a cancer cure.

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THE RELATION OF ANTECEDENT TUBERCULOSIS TO BRONCHOGENIC CARCINOMA

A Study of the Tuberculin Test, Radiologic and Pathologic Evidences

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SINCE the first description of coexistent bronchogenic carcinoma and pulmonary tuberculosis by Bayle in 1810,[1] there have been several interpretations regarding the association of these two diseases. Interest in this problem has been stimulated by the recognized increase of bronchogenic carcinoma and the search for an etiologic agent. In an attempt to investigate further the possible connection between the two diseases, this present study was begun. A series of patients with primary bronchogenic carcinoma was compared with a control group with respect to the tuberculin skin test. This same group was studied radiologically to determine how often the calcified, primary tuberculous complex was associated anatomically with tumor; and both lesions were classified as to segmental location. This segmental localization of bronchogenic carcinoma was confirmed by the examination of an additional series of resected pulmonary carcinomas and, in a portion of these, a search was made for both calcified and noncalcified tuberculous foci.

Although Bayle usually is credited with the first documentation of these two diseases in the same patient, he used the term "phthisic," without pathologic proof, to describe a clinical state. Therefore, Penard,[2] in 1846, may have reported the first case of coexistent bronchogenic carcinoma and pulmonary tuberculosis. Since then, besides individual case reports, the literature has been concerned with three general theories: that tuberculosis and carcinoma are (1) antagonistic, (2) related coincidentally, and (3) definitely associated.

Antagonism.—Rokitansky,[3] in 1854, stated that the two diseases were antagonists since neither seemed to affect the same organs. The problem was analyzed statistically by Pearl,[4] in 1929, with a study of 6,670 postmortem records from the Johns Hopkins Hospital. In 816 autopsies of patients dying from a malignancy, 6.6 per cent had associated tuberculosis, as opposed to 16.3 per cent in the same number of persons dying from diseases other than a

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Received for publication March 2, 1959.
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malignancy. Conversely, 1.2 per cent of 886 autopsies on persons dying from tuberculosis had a cancer as opposed to 9.13 per cent in the same number dying from diseases other than tuberculosis. He supported Rokitansky's view, and even suggested treating carcinoma with iatrogenic tuberculosis. In the same year, Carlson and Bell[5] challenged Pearl's interpretation since patients usually have only one major disease: there must be more cases of tuberculosis among patients without cancer (including tuberculosis as a disease group) than in those with cancer. Then, in addition to verifying Pearl's statistics, they also noted that healed tuberculous lesions were found with approximately the same frequency in patients with cancer, active tuberculosis, and heart disease (as an arbitrary control group). Hueper[6] reviewed the previous literature and came to the conclusion that the two diseases were antagonistic, notwithstanding Carlson and Bell's conclusions. Recently, Desmueles[7] has reported the rarity, in his experience, of associated pulmonary tuberculosis and bronchogenic carcinoma.

Coincidence.—In 1932, Cooper[8] summarized the previous literature, and reported 24 cases of coexistent diseases. He concluded that "nearly all observers are agreed that healed tuberculous lesions are found with equal frequency in cases with carcinoma and in cases without carcinoma. Therefore, apparently, a latent tuberculous infection is without bearing on the development of malignant tumors." He also felt that the same was true of active tuberculosis. Earlier, Hoffman[9] reported that he could find no association and, in 1938, Holman[10] remarked: ". . . usually there is no evidence of anatomic relationship between the two processes, and more often than not the tuberculous lesions are entirely inactive." Stein[11] expressed the same opinion but presented no data. Drymalski[12] reported that in 15 (20 per cent) of 56 cases of bronchogenic carcinoma there were acid-fast bacteria on sputum analysis, but on pathologic examination only one third of these demonstrated active tuberculosis. In one half, no demonstrable tuberculous focus could be identified other than calcified nodes. He concluded that the association of the two diseases was fortuitous since he believed 10 to 20 per cent of adults dying of causes other than carcinoma of the lung have acid-fast bacteria in the sputum, and approximately 5 to 10 per cent of the population of the United States harbor living tubercle bacilli.

Definite Association.—In 1919, Broders[13] summarized all the available literature and found that the two diseases were associated in 16.3 per cent. He felt the facts did not support Rokitansky and suggested that pathologists were not searching specifically for healed tuberculous foci. Ewing, in 1928, stated that tuberculosis was the chief etiologic factor in bronchogenic carcinoma, but later modified that view (1940).[14] Barron[15] incriminated old tuberculous scars and cavities as precancerous lesions; and Fried supported this opinion. He reported that 10 per cent of pulmonary carcinomas were associated with tuberculosis[16] and, in a presentation of 13 cases,[17] named the proliferation of bronchial epithelium into tuberculous cavities as the exciting cause of carcinoma. In his opinion, old scars were invaded secondarily. Robbins,[18] quoting

unpublished data, reported that 5 per cent of 100 bronchogenic carcinomas at autopsy were associated with active tuberculosis and, in presenting 11 cases, found only 2 in which the tumor arose from an old fibrocaseous focus. In the remaining specimens, the tuberculous foci were either distal to the neoplasm or far removed from it. The view that carcinoma activates previous tuberculous lesions has been supported by Nuessle,[19] whereas the opposite view has been stressed by Woodruff,[20] who, in 67 cases, studied the anatomic relationship between pulmonary carcinomas and calcified nodules. The association was considered significant if the nodule was (1) greater than 4 mm. in size, (2) in the same lobe or lymph nodes draining the same lobe as the tumor, and (3) larger than any other nodules in the opposite lung. With the use of ante- and postmortem x-rays he noted that 79 per cent of epidermoid, 60 per cent of anaplastic, and 17 per cent of adenocarcinomas were associated closely with calcified nodules. He pointed out that the possible etiologic factors secondary to tuberculosis could be bronchial irritation by calcified lymph nodes, parenchymal scarring by a healed focus, local bronchiectasis aiding the localization of tars from cigarette smoke, and the carcinogenic activity of cholesterol frequently seen in healed foci. Schwartz[21] believes that tuberculosis is the chief etiologic factor in bronchogenic carcinoma. In a pathologic study, he has found carcinomas related to bronchial scars presumably the result of tuberculous bronchitis or adenitis. Certainly tuberculous nodes can affect adjacent bronchi, and Haggenmuller[22] has reported that, in 8.7 per cent of 987 cases of thoracic lymph node tuberculosis, there were radiologic signs of atelectasis secondary to bronchial compression or obstruction. The tubercle bacillus has been cited as causing carcinoma in mice in a single experimental study.[23] Cruickshank[24] has shown statistically that the distribution of tuberculosis closely follows that of bronchogenic carcinoma in adjacent population areas in England. Westergren[25] recently reported that 33 per cent of 100 cases of bronchogenic carcinoma developed in a part of the lung which had been previously the site of a tuberculous process. In 11 cases there was the possibility of direct association.

Minute peripheral tumors have been described by several investigators. Raeburn[26] found small, asymptomatic, malignant tumors adjacent to lung scars. He believes many carcinomas have a bronchiolar origin arising as malignant change in reparative bronchiolar hyperplasia. This has been noted to occur in association with scars of healed tuberculosis, infarcts, and foreign bodies among others. This epithelial change has been termed "benign atypical proliferation" by some authors[27] although there are 3 cases of proved lymph node metastases.[29] Raeburn has demonstrated the early spread of cancer from these peripheral growths to regional lymph nodes and lobar bronchi, thereby appearing primary in these hilar structures. Prior and Jones[30] have described minute peripheral tumors, one associated with a healed tuberculous scar. James and Pagel[31] described 2 cases of superior sulcus tumors arising from calcified apical plaques. Other observers have reported microscopic foci of tumor cells in the peribronchial fibrosis accompanying bronchiectasis.[28] These have resembled oat cell tumors, quite distinct from the bronchial squamous metaplasia associated with bronchiectasis, which has been shown rarely to cause carcinoma.[32] In these

collected studies, the malignant nature of the tumors is not well established. There is an undeniable implication, however, that tuberculosis, among other scar-producing factors, may excite the formation of some pulmonary carcinomas.

The present study may be divided into several parts: (1) tuberculin studies of comparable groups with concomitant radiologic search for evidence of tuberculous lesions, (2) pathologic studies of the surgically resected tumors in the carcinoma-tuberculin test group, and finally (3) pathologic studies of an ancillary and unrelated group of surgically resected pulmonary carcinomas.

I. TUBERCULIN STUDIES

Methods.—One hundred consecutive case histories of bronchogenic carcinoma were reviewed in which the tuberculin skin tests had been reported on the clinical record. Included in the data collected for each patient were the age, sex, smoking habit, past history of tuberculous contact or infection, and the histologic type of carcinoma and its operability. The tumors were divided into the usual four groups: epidermoid (including differentiated and undifferentiated forms), adenocarcinoma, anaplastic, and bronchiolar carcinoma. The diagnoses were made on resected tissue, node or tumor biopsies, or cytologic examination of the sputum.

Tuberculin skin tests, using purified protein derivative (PPD),* were given to one hundred males in the same general age groups as those with bronchogenic carcinoma. This control group consisted of in-patients on the surgical service of New Haven Hospital, and no note was made of the specific diagnosis in each case. No patient, however, had active tuberculosis or known bronchogenic carcinoma at the time of testing. Injections were made intracutaneously on the flexor surface of the forearms, using 0.00002 mg. Reference PPD as the first strength. Second strength dosage (0.005 mg. Reference PPD) was administered when the first strength elicited no reaction. The reaction was classified as positive when there was one centimeter or more induration and erythema at the site of injection. The smoking history was based only on whether or not the patient had smoked cigarettes rather than the degree of smoking. Positive tuberculosis histories were based on proved infection and not "pleurisy," "consumption," and the like.

TABLE I

	CANCER GROUP (%)	CONTROL GROUP (%)
Positive PPD	95	80
Previous known contact with tuberculosis	20	11
Previous clinical tuberculous infection	2	3
Cigarette smokers	86	77

Results.—Ninety-five per cent of the carcinoma group had positive tuberculin reactions as opposed to 80 per cent of the control. There was a greater correlation between bronchogenic carcinoma and the positive tuberculin reaction

*Parke, Davis & Co., Detroit, Mich.

than with cigarette smoking. Eighty-six per cent of the carcinoma group and 77 per cent of the control group were smokers (Table I). For statistical analysis of the tuberculin reactions in both groups, the chi square test was applied. The result ($\chi = 10.29$) demonstrated significance well beyond the 0.01 level; this result would be obtained by chance much less frequently than one time in a hundred ($p < 0.01$).

The control and carcinoma groups had similar decade distributions (Table II). The mean ages were essentially identical: 60.7 years for the control, and 60.1 years for the carcinoma groups. The number of negative reactors in each decade in the control group was fairly constant (Table III). The 5 cases in the carcinoma group with negative tuberculin skin tests were composed of the following: 2 were in the eighth decade,[35, 36] and 2 in the sixth decade without contact histories of tuberculosis. The final case was in the fifth decade and had an extensive family and contact history of tuberculosis. All but one were cigarette smokers. It should be noted that testing in the carcinoma group was done by various contemporary, unselected members of the house staff at this hospital rather than by a single individual as in the control group. The error in observation in the carcinoma group, if any, showed favor for a higher number of negative reactors since Ghon complexes were demonstrable radiologically in 2 of the 5 patients who had negative tuberculin skin tests (see Section II).

TABLE II. TUBERCULIN SKIN TEST

DECADE	NUMBER OF PATIENTS	
	CARCINOMA GROUP	CONTROL GROUP
3-4	3	4
4-5	10	13
5-6	30	30
6-7	36	45
7-8	21	8
Totals	100	100

TABLE III. TUBERCULIN TESTS (CONTROL GROUP) DISTRIBUTION OF NEGATIVE REACTORS

DECADE	NUMBER OF NEGATIVE REACTORS
4-5	2
5-6	5
6-7	7
7-8	6

Of the carcinoma group there were 50 epidermoid, 24 anaplastic, 15 adeno-, and 2 bronchiolar carcinomas. Nine had no definite tissue type diagnosis; 7 of these were inoperable and 2 had negative biopsies on exploration. The subsequent lethal course, however, favored the diagnosis of bronchogenic carcinoma.

II. RADIOLOGIC STUDIES

Having found that 95 per cent of patients with bronchogenic carcinoma had had a previous tuberculous infection as demonstrated by the positive tuberculin skin test, an attempt was made to determine if there was anatomic

and radiologic association between tumor and tuberculous focus. Association was defined as positive when both lesions occupied the same pulmonary segment, or when a hilar tumor had adjacent tuberculous lymph nodes. The study was carried out on the above 100 cases of bronchogenic carcinoma, and involved a topographical classification of the tuberculous lesions and tumors according to pulmonary segments.

Methods.—Chest films were available in all the carcinoma-tuberculin test group. In most instances, these included planigrams as well as standard projections. Primary tuberculous foci were defined as isolated or multiple areas of discrete calcification in the lung fields, with or without hilar calcification. The latter when seen alone was considered part of the primary complex. It was realized that the differentiation between calcified tuberculous and other granulomatous foci is impossible on radiologic grounds. Secondary tuberculous infection was identified as unilateral or bilateral, fibrous or fibrocalcific densities localized to the upper lung fields, under the supposition that 90 per cent of reinfection tuberculosis occurs in the apices. It was appreciated that other nontuberculous pneumonic processes may have residual apical fibrosis in isolated instances.

An attempt was made on the basis of the x-ray studies to place the tumors in the usual ten pulmonary segments or the major bronchi. In tabulating the results, the lingula was considered as the left middle lobe. Some difficulty was encountered in the placement of large neoplasms involving the entire upper lobes. These were classified as "upper lobe unspecified." No similar difficulty was noted with middle or lower lobe tumors.

Results.—Primary tuberculous foci were seen radiologically in 47 per cent of the series. Two of the 5 patients with negative tuberculin tests had well-defined primary foci, and 2 others had "questionable primaries." In only one was there no suggestion of a primary lesion. The results of these 5 cases were not included in the 47 per cent incidence of primary foci, since the negative tuberculin reaction suggests that these foci might be other granulomata. Included in the group, however, were 2 cases of disseminated foci (Table IV).

TABLE IV. RADIOLOGIC LOCALIZATION OF CALCIFIED PRIMARY TUBERCULOUS FOCI IN 100 CASES OF BRONCHOGENIC CARCINOMA

Complete complexes	7
Incomplete complexes	38
Disseminated complexes	2
Total	47

Complete Ghon complexes were seen in only 7 cases, hilar calcification alone in 23 cases, and parenchymal foci without demonstrable hilar components in 15 cases. Thus, incomplete complexes were seen in 38 of the 100 cases, and parenchymal foci visualized in 22 of the group.

The segmental distribution of the *parenchymal* foci is seen in Table V. Segments were involved with equal frequency, and the higher number in the apical lower lobe segments is probably not significant. The upper lobe segments

were involved in only 4 cases, amounting to 18 per cent of the 22 cases. This contrasts markedly with the incidence of neoplasms in the upper lobes, which is discussed in the following section.

TABLE V. CALCIFIED PRIMARY TUBERCULOUS FOCI
SEGMENTAL LOCALIZATION IN 45 CASES

SIDE	HILAR ONLY	B^1	B^2	B^3	B^4	B^5	B^6	B^7	B^8	B^9	B^{10}
Right	12	1	1	1	3	0	3	0	0	0	3
Left	11	1	0	0	0	1	4	2	0	2	0
Totals	23	2	1	1	3	1	7	2	0	2	3

In 15 of the 100 cases there was definite radiologic evidence of re-infection tuberculosis, all in the upper lobes. In an additional 3 cases, there was questionable tuberculous re-infection, and these are not included in the data for this group (Table VI). There were 13 cases of tuberculosis in the right upper lobe, and 2 in the left upper lobe. Forty-seven per cent of the 15 tumors in this group were in the apical upper lobe segments. Two tumors (13.3 per cent) were in the superior lower lobe segments. All of these patients had positive tuberculin reactions, and there were 7 epidermoid, 6 anaplastic, and one adenocarcinoma. One patient had no positive tissue diagnosis of cancer. All but one were cigarette smokers, and only one had a contact history of tuberculosis. During hospitalization, 2 patients had acid-fast bacteria seen on smear, and in 4 no sputum examinations were carried out. One patient, not included in the 15, had a positive sputum culture for tubercle bacilli but no demonstrable lesion radiologically.

TABLE VI. RE-INFECTION TUBERCULOSIS
RADIOLOGIC DIAGNOSIS IN 15 CASES

	TUMOR LOCATION			
	B^1	B^2	B^3	B^6
Numbers	7	3	0	2
Per cent of group	47.0	20.0		13.3

In only 10 of the 100 cases could an anatomic-radiologic association of tumor and tuberculous lesion be established. No parenchymal primary foci were noted in the tumor segments, but there were 7 instances of tumors adjacent to calcified nodes. Three of the patients with re-infection tuberculosis had anatomic association of tumor and tuberculous foci, and Table VII summarizes those findings. There was the tendency not to identify primary and re-infection lesions in the tumor segments. It was assumed that distal infiltrates, or dense, discrete foci, most likely represented tumor itself or distal parenchymal changes secondary to neoplastic obstruction.

TABLE VII. RADIOLOGIC LOCATION OF TUMOR AND RE-INFECTION TUBERCULOSIS IN 15 CASES

3 (20%)	In the same segment
4 (26.7%)	In the same lobe
10 (66.7%)	In the same or contralateral upper lobe

III. PATHOLOGIC STUDIES OF THE RESECTED SPECIMENS IN THE CARCINOMA-TUBERCULIN TEST GROUP

Thirty-eight cases in the 100 comprising the carcinoma-tuberculin test group were subjected to the removal of a lobe or lung. Of these, 33 specimens were still available for study. A careful inspection was carried out to determine evidence for tuberculosis, beyond that revealed in the roentgenograms, and to evaluate the radiologic segmental localization of the tumors. It was noted that the radiologic placement was incorrect in one third of the 33 cases. In an attempt to establish a more accurate topographical classification, 142 additional and unrelated, surgically resected, pulmonary carcinoma specimens were examined for tumor location.

Methods.—The segmental location of all previously resected tumors was a relatively easy matter since it has been routine in the Department of Pathology to section all lungs along the bronchial planes. In this technique, all the bronchi, including the one involved by tumor, are exposed meticulously. In the present study, difficulty in segmental placement was encountered only with some hilar tumors presenting a distal extension. In many cases, neoplasms apparently taking origin in the periphery had stalk-like projections to the hilar structures. It was considered reasonable to assume that these involved the major bronchi only secondarily.[39] Hilar tumors without larger peripheral components were considered primary in the involved bronchus. The limitation of this approach is appreciated.

The 33 resected specimens in the original carcinoma-tuberculin test group were studied for evidence of coexistent tuberculous infection. This was done without further damage to the specimens which, on account of previous sectioning, consisted of approximately one half the original tissue mass. Microscopic examination of subpleural nodules, calcified hilar nodes, apical scars, and suspicious regions, adjacent to the tumors, was carried out when indicated by gross examination. Actually, only one third of the specimens had grossly demonstrable lesions warranting microscopic section. It was understood well that tuberculosis is a bacteriologic diagnosis, and that hyalinized scars and calcified nodules or nodes are only presumptively tuberculous. Apical scars and calcifications were not considered tuberculous, per se.[33]

Results.—The pathologic re-examination of these 33 specimens from the carcinoma-tuberculin test group gave additional tuberculosis data beyond that accumulated by radiography. In 8 cases, 9 types of lesions, not established by roentgen ray, were discovered; these are listed in Table VIII. Most interesting was the finding of 2 additional instances of re-infection tuberculosis associated with the tumors. Both patients had had re-infection tuberculosis diagnosed radiologically but on the side opposite from the tumor. Another patient had had a peripheral, hyalinized scar related to the tumor, and a final one had had a calcified node associated with a hilar tumor. Adding these 4 cases of pathologically associated tuberculosis and carcinoma to the 10 diagnosed radiologically brings the total to 14 per cent for the entire 100 cases.

TABLE VIII. ADDITIONAL TUBERCULOSIS FINDINGS ON ANATOMIC STUDY IN 33 CASES OF RESECTION

	OCCURRENCE
Apical calcification	1
Multiple calcified foci	1
Calcified node associated with tumor	1
Hyalinized scar associated with tumor	1
Several hyalinized foci	1
Re-infection tuberculosis in additional segments	2
Tumors associated with re-infection tuberculosis	2

Since anatomic placement of the tumors appeared to be more accurate than radiologic placement alone, the 33 resected tumors were supplemented by 142 unrelated carcinoma specimens, totaling 175, for anatomic study. These are compared with the remaining 67 nonresected tumors in the x-ray studies of the original carcinoma-tuberculin test group in Table IX. There was fairly close agreement with the exception that fewer tumors were considered primary in the major bronchi on gross examination. Twenty-one per cent of the neoplasms were primary in the hilar and lobar bronchi, and 79 per cent had obvious segmental or subsegmental origin. The predilection of bronchogenic carcinoma for particular regions contrasts with the apparent haphazard distribution of the primary parenchymal tuberculous focus as noted in the previous section, and summarized in Table V.

TABLE IX. BRONCHOGENIC CARCINOMA

CASES	ULB	B^1	B^2	B^3	UL UNSPEC.	B^4	B^5	RIB
				Segmental Location				
67 (x-ray)								
Right side	2	5	3	6	3	0	1	3
Left side	2	4	6	5	3	1	2	—
(Per cent)	(6)	(13.5)	(13.5)	(16.3)	(9.0)	(1.5)	(4.5)	(4.5)
175 (gross)								
Right side	3	21	15	17	1	2	2	7
Left side	7	9	19	13	1	2	2	—
(Per cent)	(5.7)	(17.2)	(19.4)	(17.2)	(1.1)	(2.3)	(2.3)	(4.0)
Totals								
242	14	39	43	41	8	5	7	10
(Per cent)	(5.8)	(16.1)	(17.8)	(16.9)	(3.3)	(2.1)	(2.8)	(4.1)

CASES	MSB	LLB	B^6	B^7	B^8	B^9	B^{10}
			Segmental Location				
67 (x-ray)							
Right side	3	3	0	0	0	0	0
Left side	2	7	5	0	0	0	1
(Per cent)	(7.5)	(15.0)	(7.5)	(0)	(0)	(0)	(1.5)
175 (gross)							
Right side	1	5	17	5	1	1	2
Left side	0	6	7	1	1	2	5
(Per cent)	(0.6)	(6.3)	(13.7)	(3.4)	(1.1)	(1.7)	(4.0)
Totals							
242	6	21	29	6	2	3	8
(Per cent)	(2.5)	(8.7)	(12.0)	(2.5)	(0.8)	(1.3)	(3.3)

Legend: MSB = main-stem bronchus; RIB = intermediate bronchus; ULB = upper lobar bronchus; LLB = lower lobar bronchus.

The variance of segmental placement by gross dissection as compared with radiologic means for the 33 resected cases is summarized in Table X. In view

of the discrepancy noted, roentgen analysis of the tumor site was carried out again. Films of 10 of the 12 patients cited were available for re-evaluation. In 2 cases it was found that more exact localization could have been made from information present in the films. The roentgen localization remained unchanged in 5 cases, the exact position of the tumor being masked by associated atelectasis or pneumonitis. This was particularly true where a tumor arose in a proximal segmental region close to the hilum. As indicated in other studies,[40] the clinical manifestations of the tumor which brought the patient to x-ray examination were not present until a lobar bronchus or the right intermediate bronchus (see Case 3, Part II, Table X) had been encroached upon. When this occurs, definition of the origin of the tumor is extremely difficult or impossible. In the remaining 3 cases it was felt that the localization had been made with insufficient radiographic studies.

TABLE X. VARIATIONS IN X-RAY AND GROSS TUMOR PLACEMENT IN 33 CASES

I. 4 Cases Segmental	
X-Ray	*Gross*
B^2	B^3
B^{10}	B^6
B^9	B^7
B^3	B^1
II. 6 Cases Hilar and Lobar	
X-Ray	*Gross*
ULB	B^3
ULB	B^2
RIB	B^6
LLB	B^3
LLB	B^6
MSB	ULB
III. 2 Cases Upper Lobe Unspecified	
X-Ray	*Gross*
Unspec.	ULB
Unspec.	B^3

IV. PATHOLOGIC STUDY OF 50 UNRELATED SURGICALLY RESECTED BRONCHOGENIC CARCINOMAS

Finally a macro- and micropathologic study of 50 additional resected specimens, not in the carcinoma-tuberculin test group, was undertaken to investigate further the incidence of associated pulmonary tuberculosis and bronchogenic carcinoma.

Methods.—This examination was carried out in similar fashion to the previous pathologic studies, and histologic sections were taken only when indicated on gross examination. Sectioning was done carefully in such a way as to preserve the specimens, which again consisted of only one half the original tissue mass.

Results.—Five types of tuberculous lesions were found in 25 cases. The remaining 25 did not appear to warrant microscopic sectioning. In the latter group, approximately one half were hilar or lobar bronchial tumors, and most of the adjacent lymph nodes had been extirpated previously. Table XI lists

the kinds of tuberculous lesion noted, and the numbers of tumors in anatomic association. Multiple, hyalinized, focal scars were noted in 5 cases, and single, hyalinized foci in 4 cases. None of these was anatomically associated with the respective tumors. Fibrocaseous, re-infection tuberculosis was noted in 5 cases (10 per cent), but only 4 cases (8 per cent) were positively related to the tumors. There were 2 cases of calcified nodes adjacent to hilar tumors and, in one instance, a subpleural calcified nodule was found less than one centimeter from a peripheral tumor. Thus, there were 7 instances (14 per cent) of positively associated tuberculosis and bronchogenic carcinoma. This agreed exactly with the results reported in Section III.

TABLE XI. 50 CONSECUTIVE SPECIMENS

LESION	OCCURRENCE	TUMOR ASSOCIATION
Calcified nodule	3	1 (2%)
Calcified node	4	2 (4%)
Single hyalinized scar	4	0
Multiple hyalinized scars	5	0
Re-infection tuberculosis	5	4 (8%)
Totals	21	7 (14%)

The breakdown of associated lesions in this group and the original carcinoma-tuberculin test group was only slightly different. In the original group, 5 per cent had associated re-infection tuberculosis as opposed to 8 per cent in the supplementary group. Eight per cent of the original group had tuberculous adenitis associated with hilar tumors as opposed to 4 per cent in the supplementary group. One of the original carcinoma group had an associated hyalinized scar, and one of the supplementary group had an associated calcified nodule.

DISCUSSION

Studies of pulmonary cancer and tuberculosis, predicated only on gross and microscopic examination of tissue may be misleading since tuberculosis is a disease based on a bacteriologic diagnosis. For this reason, the tuberculin skin test was investigated primarily in the study, with supplementary radiologic and pathologic data.

One may conclude from these results that the tuberculin skin test, in cases of bronchogenic carcinoma, is more constantly positive than is the history of cigarette smoking. However, from these results and those of other studies, one cannot conclude that bronchogenic carcinoma and pulmonary tuberculosis are related etiologically. Even though both may at times affect the same portions of the lung, and the incidence of positive tuberculin reactors is extremely high, the lack of pathologic proof in a majority makes the assumption as yet invalid. Our criteria of positive anatomic association were more rigid than some others in the literature, notably Woodruff's whose studies demonstrated a higher incidence of association.

It seems reasonable to consider bronchogenic carcinoma as an abnormal process of epithelial regeneration in the lung. As with simple inflammation, it

may have a variety of etiologic agents. Recent studies of "lung-scar cancers" seem to support the theory that it is the scar, and only remotely the agent causing the scar, that is important in the pathogenesis of the disease. Tuberculosis is a common cause of pulmonary scars. The most frequent location of bronchogenic carcinoma in the upper lobes and the apical segment of the lower lobes suggests a relationship to *re-infection* tuberculosis. Against this, however, are the facts that (1) only 15 per cent of the cases in the carcinoma-tuberculin test group had demonstrated coexistent re-infection tuberculosis, (2) only one half of these had a positive anatomic association of both diseases, and (3) that the anterior upper lobe segment (B^2), which was a common site of carcinoma, was less commonly the seat of re-infection tuberculosis.

The haphazard distribution of the primary parenchymal tuberculous focus is not characteristic of bronchogenic carcinoma. Furthermore, 22 per cent of the 95 patients with bronchogenic carcinoma with positive tuberculin skin tests had primary parenchymal foci radiologically separate from the tumor mass. Considering such tumors to be caused by a healed focus would imply that more than one focus existed. Medlar[33] has emphasized that multiple (two or more) primaries occur in only 10 per cent of lungs which are the site of primary tuberculous infection; and this makes the theory of multiple primaries in cases of bronchogenic carcinoma less likely. There was no instance of radiologically positive anatomic association of primary *parenchymal* tuberculous lesion and tumor in the 100 cases studied radiologically. This was due partly to our reluctance to classify a dense focus near or within a tumor shadow as tuberculous. In addition, in 78 of the 95 tuberculin *positive* cases no parenchymal component of the primary tuberculous complex could be detected radiologically. Rich[38] has stressed that x-ray studies are notoriously poor in demonstrating these minute lesions. The high incidence of nonvisualization may indicate that the tuberculous foci were in fact within the tumor mass. The difficulty in finding these foci on gross examination of a large, solid tumor is obvious, and one must remember that they might be destroyed by malignant growth. Particles of calcium seen on microscopic examination of tumors not uncommonly occur as the result of local necrosis, and cannot be interpreted as remnants of tuberculous disease. Attempts to study tumors by serial sections were not carried out in the study.

The incidence of positive reactors in the control group correlates closely with the findings of other investigators dealing with mass surveys of eastern metropolitan areas.[34] The tuberculin skin test might be of greater value in areas where the positive reaction is less common than in the East. In this instance, a 95 per cent incidence of positive reactors in cases of bronchogenic carcinoma would be of even greater statistical significance.

SUMMARY

1. One hundred cases of bronchogenic carcinoma were compared with a control group with respect to the tuberculin skin reaction. Ninety-five per cent of those with carcinoma were tuberculin positive as compared to 80 per cent in the control group. This difference has statistical significance in the order $p<0.01$.

2. Primary tuberculous calcified foci were seen radiologically in 47 per cent of the 100 cases. In only 7 per cent of these were complete Ghon complexes seen. The parenchymal component was visualized in 22 per cent of cases, and had a random distribution as regards pulmonary segments.

3. Re-infection tuberculosis was noted radiologically in 15 per cent of the bronchogenic carcinomas studied.

4. Positive anatomic association was defined as (a) their co-situation in the same segment, or (b) the approximation of tumor and a calcified hilar node. On radiologic and gross examination, this was noted in 14 per cent of the 100 cases studied.

5. The segmental distribution of bronchogenic carcinoma was tabulated on radiologic examination of 67 of the 100 cases, on gross examination of 33 resected specimens of the same series, and 142 unrelated, additional specimens. The predilection of tumors for the upper lobe and superior lower lobe segments was noted. The upper lobe segments were all involved, and with equal frequency.

6. Segmental placement of tumors by radiologic means may be misleading with certain peripheral neoplasms having extensions to major bronchi. In such instances, associated atelectasis and pneumonitis may mask the actual position of the tumor.

7. The possible relationship of bronchogenic carcinoma to antecedent tuberculosis is discussed with particular reference to the primary and reinfection types of lesions.

8. The shortcomings of a purely statistical approach to tumor pathogenesis is well demonstrated.

ADDENDUM

Since this study has been compiled, an additional 28 consecutive patients with pulmonary carcinoma, admitted to the Thoracic Surgical Service, have been subjected to the tuberculin skin test. In every case the reaction was positive, using the same criteria stated in Part I of this report.

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LEIOMYOMA OF INTERMEDIATE BRONCHIAL ORIGIN

A Case Report

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BENIGN mesodermal tumors originating from intermediate bronchi are extremely rare. Most lesions of this type originate in main-stem bronchi. According to Liebow,[1] fibromas and chondromas are the most frequent tumors, accounting for from 80 to 90 per cent of benign intrabronchial tumors. In 1955, Hirose and Hennigar[2] reported only the third case of intrabronchial leiomyoma, and extensively summarized the literature. Because of the rarity, the following case is reported.

CASE REPORT

A 43-year-old white housewife was admitted to the hospital on Dec. 9, 1958. Five months previously she had developed an upper respiratory infection. Following the infection she noted a persistent cough, which was productive of thick, yellowish mucus. She also complained of intermittent pain over the right chest, which was aggravated by deep inspiration. The past medical history was unremarkable, and no previous operations had been performed.

Physical examination disclosed a temperature of 99° F., pulse rate of 80, respiration rate of 20, and blood pressure of 140/90 mm. Hg. Slight dullness and absent breath sounds over the right lung base were the only significant physical findings.

Laboratory studies, including red and white cell count, hemoglobin determination, and urinalysis, were in the normal range. An electrocardiogram was interpreted as within normal limits.

Roentgenogram of the chest disclosed a right pleural effusion, partial atelectasis of the right middle and lower lobes, and definite elevation of the right leaf of the diaphragm.

On the second hospital day, bronchoscopy was performed by one of us (J. T. S.). A rounded smooth mass was observed projecting into the lumen of the right intermediate bronchus, approximately 1 cm. below the inferior spur of the right upper lobe. The lesion produced virtually complete obstruction of the right middle and lower lobe bronchi. The mass was biopsied and partially resected.

Histologic examination revealed a benign leiomyoma. The patient was discharged on the fourth hospital day to be readmitted at a later date for further definitive therapy.

She was readmitted to the hospital one month later. Her clinical condition had remained unaltered. The chronic cough persisted and had not changed in character. Physical findings at this time again revealed dullness and absent breath sounds over the right lung base. A few moist râles, and an inspiratory wheeze were audible over the right upper posterior lung field. Laboratory data and chest roentgenogram were unchanged. Preoperatively the patient received streptomycin and penicillin therapy.

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Received for publication March 11, 1959.

On the third hospital day, thoracotomy was performed (J. T. S.). The right lower lobe was adherent to the diaphragm, and the right middle lobe to the anterior chest wall. There was complete atelectasis of the right lower lobe, and partial atelectasis of the right middle lobe. Because of marked suppuration and obstructive pneumonitis, the right middle and lower lobes were removed.

The postoperative course was uneventful. Antibiotic therapy was continued, and the patient was discharged on the nineteenth hospital day.

Pathology.—Grossly, the resected specimen consisted of the right middle and lower lobes with a total weight of 100 grams. The pleural surface of both lobes was roughened and thickened. Dissection of the bronchi revealed, within the right intermediate bronchus, a polypoid tumor, 1.2 cm. in diameter, arising from the submucosal region. The external surface was smooth, homogeneous, gray-white, and slightly lobulated (Fig. 1). The tumor had produced complete obstruction of the bronchial lumen. The main bronchi of both

Fig. 1.—Gross photograph showing polypoid intrabronchial tumor.

lobes were markedly dilated down to the terminal portions. The mucosa was roughened, granular, and contained purulent gray-yellow exudate. The adjacent lung parenchyma showed extensive pneumonitis of obstructive type. The hilar lymph nodes were moderately enlarged.

Microscopic examination: Sections of the bronchoscopic specimen, and the lesion from the lobectomy showed an identical structure. The tumor was observed to originate just beneath the submucosa of the bronchus. A thin, but definite fibrous capsule was present (Fig. 2). Slight squamous metaplasia was noted in the overlying bronchial mucosa. The neoplasm was composed of elongated spindle-shaped cells, which appeared to represent a mixture of smooth muscle and fibroblastic types. In some regions, definite palisading of nuclei was observed. Individual nuclei were fairly uniform and regular, and excessive mitotic activity was not present (Fig. 3). Specific stains by the van Gieson and trichrome methods demonstrated that the predominating cells were of smooth muscle type. A sparse fibrous, or collagenous component was also apparent. The histologic pattern was consistent with a benign leiomyoma of bronchial origin.

Sections of lung parenchyma confirmed the impression of chronic interstitial pneumonitis of obstructive type, and also showed extensive bronchiectasis. The hilar lymph nodes showed only anthracotic pigmentation.

Fig. 2.

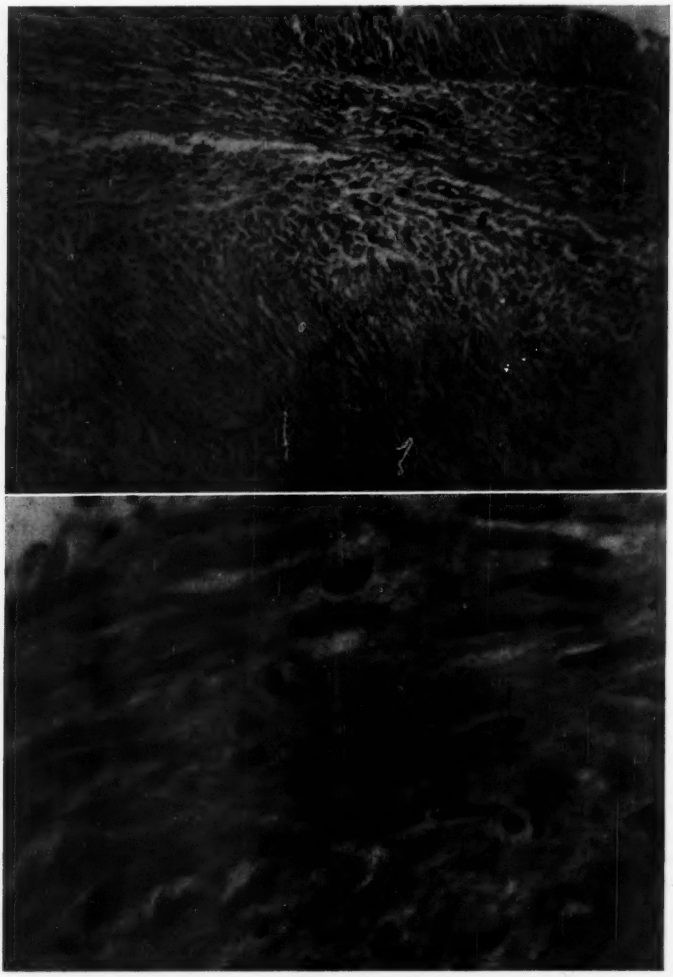

Fig. 3.

Fig. 2.—Photomicrograph showing the origin of leiomyoma in submucosal zone of the bronchus (×160).

Fig. 3.—Higher power photomicrograph showing details of cell morphology (×320).

DISCUSSION

There is no doubt that the present case is representative of benign intrabronchial leiomyoma. There was no evidence of parenchymal origin. The

location and histologic features preclude a metastatic lesion. Hamartomas may occasionally contain large elements of smooth muscle, but admixtures of other mesodermal components aid in the diagnosis.

Other types of intrabronchial tumors have been described. Liebow[1] states that lipomas, lymphoma, myoblastoma, and even a plasmocytoma have been recorded. Primary leiomyosarcoma may occur, but is likewise extremely rare.[3] The cellular morphology of the present case was not typical of leiomyosarcoma, although differentiation is not always made with ease.

The histologic features of the present case are very similar to the case described by Hirose and Hennigar.[2] The latter authors were able to find only 2 previous cases of intrabronchial leiomyoma, although six instances of parenchymal origin were found. The principal features which were of aid in the differentiation of leiomyoma from other more common bronchial tumors was adequately discussed.

Clinically, it is apparent that the symptoms of bronchial leiomyoma may resemble those of bronchial adenoma. Pneumonitis of obstructive type is common to both lesions, and is directly responsible for many of the clinical symptoms. If prolonged bronchial obstruction continues without surgical intervention, bronchiectasis may follow as a secondary complication.

The treatment of bronchial leiomyoma will vary according to factors affecting the individual case. The site of origin, malignant potentialities of the neoplasms, the presence of secondary complications, such as bronchiectasis or extensive pneumonitis, are factors which must be considered. If the tumor is confined to a small focus, adequate wide resection would be appropriate. In the presence of extensive bronchiectasis and pneumonitis, however, lobectomy may be necessary. On the basis of histology, irradiation therapy could be expected to offer no possible benefits.

SUMMARY

A rare case of leiomyoma of intermediate bronchial origin is presented and discussed.

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PRESCALENE FAT PAD BIOPSY

Analysis of 362 Cases

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ALTHOUGH frequent involvement of the supraclavicular lymph nodes by metastatic carcinoma of the stomach has been a well-documented clinical observation since the time of Virchow, it has been only during the past decade that the prescalene fat pads with their abundance of lymphoid tissue have been studied as a reflection of various pulmonary diseases. Since Daniels'[5] presentation, in 1949, of prescalene fat pad biopsy as a method of diagnosing certain intrathoracic diseases, several series of cases have been presented with statistical analysis of the value of this procedure as a supplemental diagnostic tool in the study of pulmonary disease.[1, 4, 10, 12] Various modifications and extensions of the simple prescalene fat pad removal have been suggested, and the lymphatic drainage of the lungs has been restudied in an effort to improve the value of this procedure as a diagnostic and prognostic procedure.[7]

In general, removal of the prescalene fat pads has been useful for two different purposes. The procedure has been used as a diagnostic aid in bronchogenic carcinoma as well as other pulmonary diseases when the conventional diagnostic methods fail to establish clearly a diagnosis. In addition, it has been used as a criterion of operability in cases of bronchogenic carcinoma, it being the opinion of most thoracic surgeons that involvement of the prescalene lymph nodes by metastatic carcinoma constitutes a contraindication to excisional surgery in most instances. Although there has been general agreement that biopsy of palpable supraclavicular nodes should be done, removal of the prescalene fat pad with its contained nodes in the absence of clinically palpable enlargement has continued to be the subject of controversy. In an effort to evaluate the diagnostic and prognostic value of this procedure, we have reviewed the experiences during the past 5 years (January, 1953-December, 1957), at the Kansas City Veterans Administration Hospital and

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Received for publication March 17, 1959.

*During the time that this work was done, Dr. Brownlee was a Fellow of the American Cancer Society and his portion of work described in this paper was done under an American Cancer Society Clinical Fellowship. Dr. Brownlee's present address is 1616 North Norton, Tucson, Arizona.

the University of Kansas Medical Center, which comprises 362 consecutive prescalene node biopsies. The combined experience has been compiled and tabulated and the experience of each hospital tabulated separately for comparative purposes.

For the most part, the procedures were done by the resident staff, often by the first or second year resident, and the technique employed (Fig. 1) consisted of simple removal of the prescalene fat pad under local anesthesia.

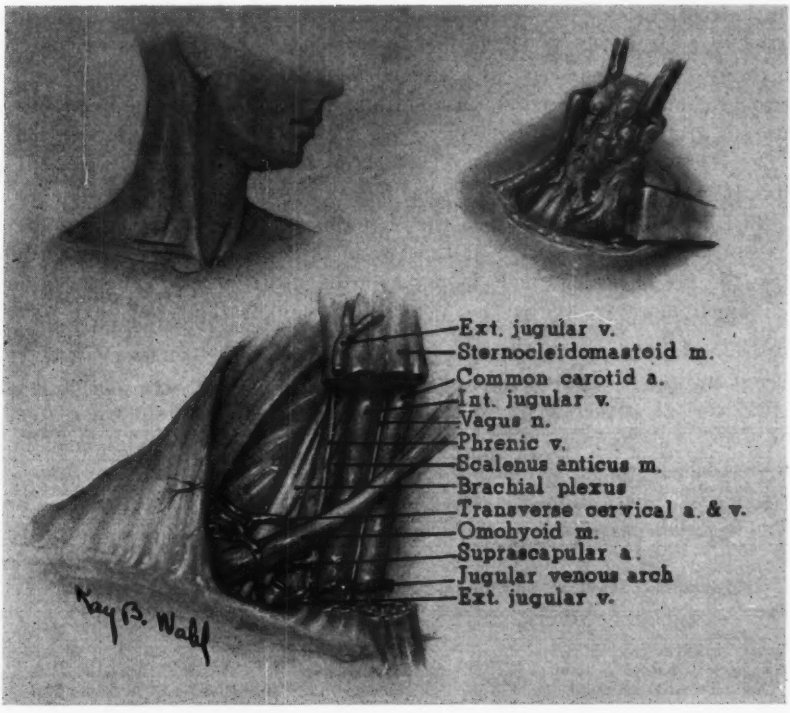

Fig. 1.—Drawing to illustrate the anatomic features of the supraclavicular triangle as well as the skin incision and removal of the prescalene fat pad.

In almost all instances, the right fat pad was removed when the right lung was involved and the left fat pad removed when the left lung was involved. Although many authors[2, 6, 9] have recommended removal of the right scalene nodes for pulmonary lesions involving the left lower lung field, based upon the lymphatic drainage patterns reported by Rouviere,[8] we have continued to remove the ipsilateral node. Serious doubt of this concept of cross drainage of the lymphatics from the left lower lobe has been raised by the recent work of Correll and Langston[3] who found an essentially ipsilateral drainage pattern by injecting dye into various areas of the dog's lung by a transbronchial

route. Likewise, the results reported by Shields, Lees, and Fox[11] of 12 per cent histologically positive nodes in their series of biopsies of nonpalpable nodes, in which bilateral fat pad removal was done in lung lesions involving the middle or lower lung field on the left side, is almost identical with the results in our study (12.7 per cent). Removal of the opposite fat pad, therefore, may be indicated when the primary lung lesion is in the left lower lobe or hilum and the ipsilateral nodes are histologically negative.

Table I contains the summary of the entire experience of the two institutions comprising 362 biopsies, of which 98 or 27 per cent were diagnostically positive; 68 or 19 per cent were positive for carcinoma, while the remaining 30 or 8 per cent were diagnostically positive for conditions other than carcinoma. Comparison of the total positive results obtained in the Veterans group and the University group shows a considerable discrepancy—21 per cent versus 37 per cent. The reason for this is readily apparent in Table II which shows the much higher percentage of clinically palpable nodes in the University group than in the Veterans group—44 per cent versus 23 per cent. During the period of time when these figures have been accumulated, the use of scalene node biopsy as a diagnostic screening test has been used much more freely by the Veterans Administration staff than by the University group.

TABLE I. TABULATION OF THE ENTIRE SERIES OF BIOPSIES WITH THE NUMBER AND PERCENTAGE WHICH WERE POSITIVE ON HISTOLOGIC EXAMINATION

	V.A.	K.U.	TOTAL
Total biopsies	224	138	362
Positive–cancer	35 (16%)	33 (24%)	68 (19%)
Positive–other than cancer	12 (5%)	18 (13%)	30 (8%)
Total positive biopsies	47 (21%)	51 (37%)	98 (27%)

TABLE II. SUMMARY OF PALPABLE AND NONPALPABLE NODES IN THE SERIES

	V.A.	K.U.	TOTAL
Total biopsies	224	138	362
Clinically palpable node	52 (23%)	60 (44%)	112 (30%)
No clinically palpable node	172 (77%)	78 (56%)	250 (69%)

Table III contains a breakdown of the findings in those patients who had a scalene biopsy done with a final diagnosis of bronchogenic carcinoma made by biopsy, operation, or autopsy. Of the 208 patient with bronchogenic carcinoma, 68, or one third, had metastatic involvement of the scalene nodes. Comparison of the findings in the two institutions again shows a fairly wide discrepancy, reflecting the fact that prescalene fat pad biopsy in the presence of nonpalpable nodes was done with much greater frequency in the Veterans Hospital group than in the University group. Even so, there were 18 instances in the total study in which the scalene nodes were involved by metastatic carcinoma in which no palpable enlargement of the nodes was present.

TABLE III. COMPILATION OF THE FINDINGS IN THE 208 PATIENTS ULTIMATELY PROVED TO HAVE CARCINOMA OF THE LUNG

	V.A.	K.U.	TOTAL
Total biopsies	224	138	362
Patients with final diagnosis of cancer	129	79	208
Scalene node histologically positive for cancer	35 (27%)	33 (42%)	68 (33%)
Clinically palpable node	22 (17%)	28 (35%)	50 (24%)
No clinically palpable node	13 (10%)	5 (6%)	18 (9%)

Table IV contains an analysis of the 208 patients having a final diagnosis of bronchogenic carcinoma with respect to the presence or absence of palpable nodes and the histologic findings in the two groups. Out of the 66 patients having palpable nodes, 50 (75 per cent) were found to be histologically positive for bronchogenic carcinoma. However, in 16 instances, the enlarged nodes were histologically negative, emphasizing that the presence of enlarged prescalene nodes in the presence of bronchogenic carcinoma is not invariably indicative of metastatic involvement. The lower portion of Table IV contains the most significant figures obtained from the entire study. Of the 208 patients in the study whose final diagnosis was bronchogenic carcinoma, 142 had nonpalpable scalene nodes on clinical examination. Of this group, 18 (12.7 per cent) were found to have histologic involvement on microscopic examination. The fact that the percentages of histologically positive nodes in the two groups were almost identical—13 per cent versus 11 per cent—is doubly significant in those patients with clinically nonpalpable nodes, since the difference in the selection of patients in the two groups, as reflected by the discrepancy in figures contained in the other tables, would have no effect on the number of histologically positive specimens in those patients having nonpalpable nodes on clinical examination.

TABLE IV. SUMMARY OF HISTOLOGIC FINDINGS IN 208 PATIENTS*

	V.A.	K.U.	TOTAL
Total patients with final diagnosis of cancer	129	79	208
Clinically Palpable Node	32	34	66
Histologically pos. cancer	22 (69%)	28 (82%)	50 (76%)
Histologically neg. cancer	10 (31%)	6 (18%)	16 (24%)
No Clinically Palpable Node	97	45	142
Histologically pos. cancer	13 (13%)	5 (11%)	18 (13%)
Histologically neg. cancer	84 (87%)	40 (89%)	124 (87%)

*The 208 patients having carcinoma of the lung have been subdivided into those having clinically palpable nodes and those not having palpable nodes with a summary of the histologic findings in the two groups.

Diagnoses other than bronchogenic carcinoma which were established by scalene fat pad biopsy are summarized in Table V. It will be noted that in 10 of the cases in the University group the diagnosis was carcinoma originating outside the lung. In all but 3 of these patients, definite pulmonary abnormalities were present on x-ray. In a recent case, done since the study

was completed, scalene lymph nodes were found to contain metastases from a papillary carcinoma of the thyroid entirely unsuspected in a man having bronchogenic carcinoma resected by pneumonectomy.

TABLE V. CONDITIONS OTHER THAN CARCINOMA OF THE LUNG DIAGNOSED BY SCALENE NODE BIOPSY

	V.A.	K.U.	TOTAL
Boeck's sarcoid	3	2	5
Tuberculosis	3	1	4
Nonspecific granuloma	3		3
Lymphoma	1	3	4
Infectious mononucleosis	1		1
Thrombosed subclavian vein	1		1
Carcinoma other than lung	0	10	10

Table VI contains a breakdown of the histologic cell types found in the scalene nodes in those patients with bronchogenic carcinoma. For simplification, the lesions were divided into squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma. The variations between the two groups of patients probably reflect a difference in the classification patterns used by the various pathologists concerned. As might be expected, there was a preponderance of undifferentiated carcinoma in the histologically positive scalene group although the number of squamous cell carcinomas and adenocarcinomas is significant.

TABLE VI. SUMMARY OF HISTOLOGIC CLASSIFICATION IN THE SCALENE FAT PADS SHOWING METASTATIC BRONCHOGENIC CARCINOMA

	V.A.	K.U.	TOTAL
Squamous cell carcinoma	7	4	11
Adenocarcinoma	9	3	12
Undifferentiated	19	26	45
Total	35	33	68

SUMMARY

The diagnostic and prognostic significance of prescalene fat pad biopsy has been determined in a study of 362 patients having this procedure during the past 5 years. The series includes 138 patients from a University Hospital and 224 patients from an associated Veterans Hospital. A comparison of the two series as well as a study of the entire group is made.

Of the 362 biopsies, 98 (27 per cent) were positive, 68 (19 per cent) for carcinoma and 30 (8 per cent) for diseases other than carcinoma.

Of the 208 patients whose final diagnosis was bronchogenic carcinoma, 68 (32 per cent) had a positive prescalene fat pad biopsy.

Of the 68 instances showing a histologic diagnosis of carcinoma, 50 (73 per cent) had clinically palpable nodes, while 18 (27 per cent) had nonpalpable nodes.

Of the 142 patients in whom the final diagnosis was bronchogenic carcinoma and who had nonpalpable nodes on clinical examination, 18 (12 per cent) were positive on histologic examination.

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AN ELECTRONICALLY CONTROLLED RESPIRATOR FOR THE EXPERIMENTAL LABORATORY

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INTRODUCTION

A RESPIRATOR, consisting of an electronic timing circuit and two solenoid valves, has been used by us in the experimental laboratory for about 7 years. For some of the earlier respirators, the electrical timing units were built by electrical technicians or by us.[3] These respirators worked well and they are still being used, but it is now much easier to build the respirator with a commercially available timer. The respirator can be assembled from a few purchased parts and some standard plumbing fittings. It will operate either on compressed air from a laboratory wall line or on gas from a tank of compressed air or oxygen.

THE APPARATUS

The apparatus is illustrated in Figs. 1 and 2. The timing unit* is a mulivibrator circuit which has been employed in various designs as a cycle timer for industrial processes. The reader will be spared description of the electronic circuits. I am not sure of the details of the circuit in this commercial apparatus but circuits of similar purpose are to be found in the non-medical literature.[1, 2] The length of a timing cycle in these devices is determined by the length of time it takes a condenser to discharge through a variable resistor. Thus, by turning a knob to change the resistance, the length of the cycle is varied. In action, the timing circuit operates a relay so that this relay is alternately on and off. The length of the on and off cycles may be varied independently in a range from a fraction of a second up to about 12 seconds.

The power supply (150 volts AC) and the electrical solenoid valve are wired to a terminal strip built in the timing unit so that one solenoid valve

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Supported in part by Research Grant No. H-2879 of the U.S. Public Health Service and by grants from the American Heart Association, the Chicago Heart Association, and the Evanston United Fund.

Received for publication Jan. 20, 1959.

*Repeat cycle timer Model No. 4, G. C. Wilson Co., Huntington, West Virginia.

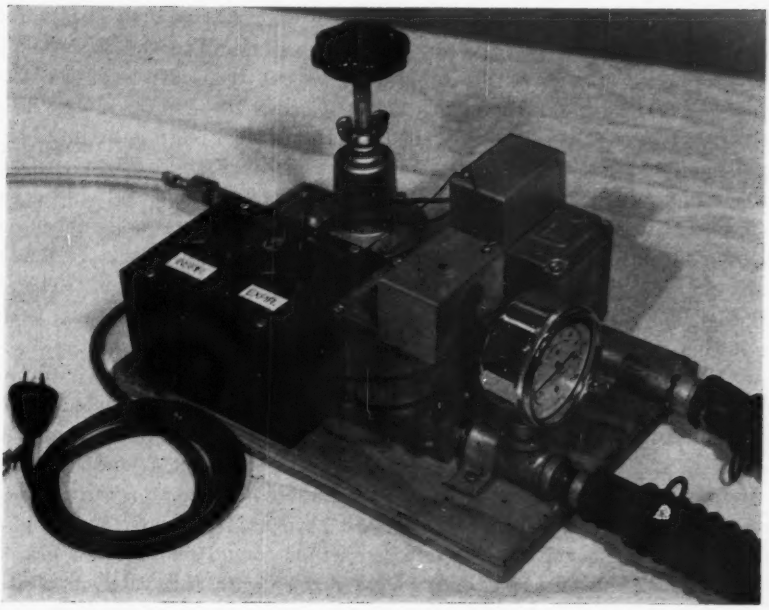

Fig. 1.—Photograph of the respirator illustrating its compact assembly on a board.

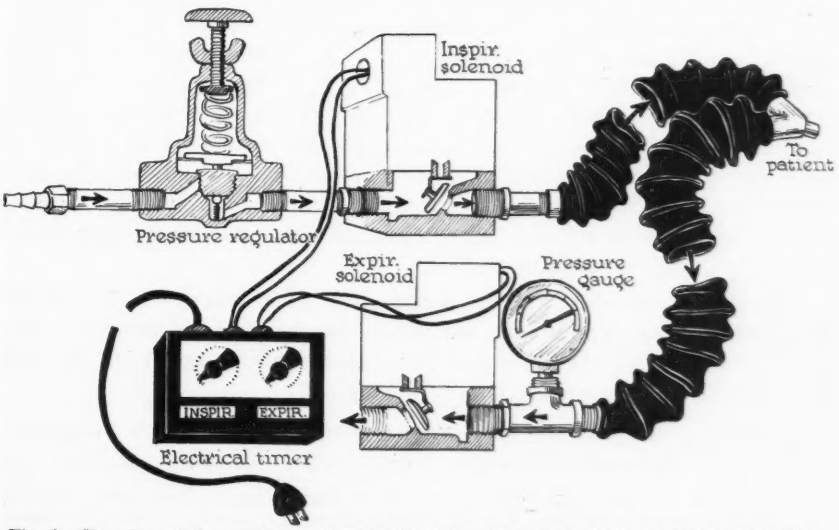

Fig. 2.—Drawing of the respirator showing the interrelationship of the various components.

receives current while the other valve is off and vice versa. The correct way of connecting the solenoids becomes relatively clear after a little study of the timing device. One solenoid becomes an inspiratory valve and the other the expiratory valve of the respirator. Thus, one of the controls of the timer regulates the length of inspiration and the other the length of expiration. The respiratory rate can be easily adjusted from 4 or 5 per minute up to more than 60 per minute, with a wide range of inspiratory and expiratory ratios. The solenoid valves,* which are identical, are normally closed and only opened when a current is applied. These valves have large apertures and rubber-cushioned flaps which make them nearly silent. If the gas pressure is too high on the inspiratory side, this type of valve will lock in the closed position. This disadvantage has not appeared with other solenoid valves we have used.† But these other solenoids are much noisier. The quiet operation of the Minneapolis Honeywell valve is worth the slight additional care necessary in controlling the inflow gas pressure. Gas entering the inspiratory solenoid must be under controlled pressure. If tank gas is used, a standard reducing valve attached to the tank is sufficient.‡ This is a pressure, not a flow rate, valve. If air from a laboratory pressure line is used, there must be a pressure-reducing valve proximal to the solenoid valve. We have used the valve shown in the illustrations.§ It is not quite as sensitive as one would like but this has been no great disadvantage. If a tank source is used with this valve in position, either it or the tank valve may be open to allow control of pressure by the other pressure regulator.

Standard pipe fittings connect the solenoids to the respirator tubing and the inspiratory solenoid to the reducing valve. The expiratory solenoid exhausts into the ambient air. Attachment of a pressure gauge‖ is a useful refinement. It allows the operator to observe the pressure in the animal's respiratory tree. Other refinements may be added as it is desired. An on and off switch has been inserted in some of these models. It is possible to hook up the resistors so that the rate and ratio adjustments may be used rather than adjustments for the length of inspiration and expiration. Grounding of the solenoids and the timer is essential if sensitive recording equipment is to be used in the laboratory.

Earlier models of this particular respirator have been used in literally thousands of dog experiments with only occasional repair problems. The model described here is newer and thus less extensively tested but it seems to be reliable. The machine is not explosion proof.

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*Silent gas valve Model No. V40A, Minneapolis Honeywell Regulator Co., Minneapolis 8, Minn.

†Valve No. V5-D1790S, Skinner Electric Valve Division, The Skinner Chuck Co., New Britain, Conn.

‡Two stage cylinder regulator, Style 8401, Air Reduction Company, New York 17, N. Y.

§Precision pressure regulator, Type 11,400, C. A. Norgren Company, 222 Santa Fe Drive, Denver 9, Colo.

‖No. 6 bag pressure indicator, Ohio Chemical and Surgical Equipment Co., 1400 E. Washington Avenue, Madison 10, Wis. (The additional fittings sold with this gauge are unnecessary.)

The same basic respirator has also been used clinically, both in the operating room and on the wards. The clinical model has some additional refinements and it is still undergoing tests and alterations.

SUMMARY

An electronically controlled respirator, consisting of a cycle timer and two solenoid valves, has been described. It is easy to assemble, reliable, and flexible in operation.

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A CARDIOVASCULAR SIMULATOR FOR THE EVALUATION OF PROSTHETIC AORTIC VALVES

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I. INTRODUCTION

THE CARDIOVASCULAR simulator described herein is a mechanical analogue of the left ventricle, aorta, and systemic circulation. It was designed to facilitate analysis of prosthetic aortic valves, and with modifications it can be used for mitral valve analysis. Potentially, the simulator is useful as a teaching and study aid, since such characteristics as peripheral resistance, aortic distensibility, etc., can be independently varied, and the effects on ventricular and aortic dynamic pressure curves immediately observed.

The resistance of a valve to blood flow, as measured by the pressure drop across it, is a function of both instantaneous flow rate and the degree of restriction. The average ejection rate during systole is only 270 ml. per second (i.e., 60 ml. stroke output ÷ 0.22 sec. ejection period) as compared to the actual peak rate of 900 ml. per second, which is developed for a small portion of the ejection time. To evaluate accurately valve stenosis, therefore, it was mandatory that the simulator duplicate the shape of the normal ventricular ejection curve as well as total stroke volume.

In order to test reliably the ability of a prosthetic valve to withstand the hydraulic forces imposed during diastole, it was also necessary to duplicate the shape of the ventricular pressure curves as well as the absolute magnitudes. The strength of materials under fatigue stress often depends on the rate of change of stress in addition to the magnitude of stress. The aortic valve is subjected to particularly high stress rates at the instant it snaps shut and must maintain diastolic pressure against the rapidly falling left ventricular pressure.

Like any system which contains a number of interdependent variables, the simulator was most conveniently designed by fixing one variable as a basic parameter. For practical reasons, the left ventricular ejection curve was selected as the parameter from which the system was to be designed. The volume and pressure curves from Wiggers[7] were used as the standard normal curves.

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Supported in part by U.S. Public Health Grant H-2774 and the Midwest Research Institute.

Received for publication March 17, 1959.

It must be noted that Wiggers' volume curve has been derived from the combined ventricular volumes. The right ventricle, lungs, left ventricle, and systemic circulation are normally in series in a closed fluid system; therefore, assuming no transient changes are taking place in the various vascular volumes, the left and right total ejection volumes per heartbeat are identical. However, the fluid dynamic "loads" (such as the magnitudes of resistance, distensibility, etc.) imposed upon the two ventricles are greatly different. Consequently, the instantaneous flow rates are different in the two pumping chambers even though the total ejection volumes are identical. This results in distortion of the shape of the volume curve when the combined ventricular volume is used to plot left ventricular ejection. Despite this inherent error, the ejection curve of Wiggers, being the most reliable data available, was used.

Austen, Shaw, Scannell, and Thurlbeck[1] have studied aortic stenosis by steady state flow versus pressure drop relationships, and Starr, Schnabel, and Mayock[6] have simulated systole in cadavers. Davila, Trout, Sunner, and Glover[2] have described a device that has the advantages of duplicating systole in a completely mechanical laboratory simulator. The instrument described below is much simpler, smaller, and less expensive to construct than that used by Davila and his co-workers, although cardiac rate and stroke output cannot be changed as easily.

II. DESCRIPTION OF APPARATUS

A. *Ventricle and Valves.*—A positive displacement pump operated at 66 strokes per minute was used as the analogue of the left ventricle (Figs. 1 and 2). The chamber consisted of a thin-walled gum rubber tube (2.4 cm. diameter by 1.5 mm. wall by 19 cm. active length) compressed between the base plate and pressure plate, the latter being actuated through a follower by a motor-driven cam. Cardiac rate could be changed by adjusting the motor gear ratio. The shape of the cam was designed so that, as it traveled through 80 degrees of rotation (22 per cent of the cardiac cycle), liquid was forced from the ventricle according to Curve 1 in Fig. 3, *A*. In order to study valves intended for dog implantation, Curve 1 (Fig. 3, *A*) is Wiggers' ejection curve scaled down to a 30 ml. stroke output. (Other stroke volumes can be obtained with different cams.) The slope of ejection curve at any instant is the ejection flow rate at that instant. Curve 1′ of Fig. 3, *B* is the derivative or "slope plot" of Curve 1 and as such it is the flow rate versus time relationship. Curves 2 and 2′ in Fig. 3 show the actual values obtained with the simulator.

The inflow end of the ventricle was fitted with a ball check valve as a mitral substitute. The outflow end of the ventricle was connected to the aortic valve holder. To establish reference curves, a ball check aortic valve was used, this being replaced by a Lucite chamber containing an experimental prosthetic valve for evaluation.

B. *Aorta.*—In normal young adult man and in the dog, an approximately straight-line relationship exists between aortic pressure and aortic volume

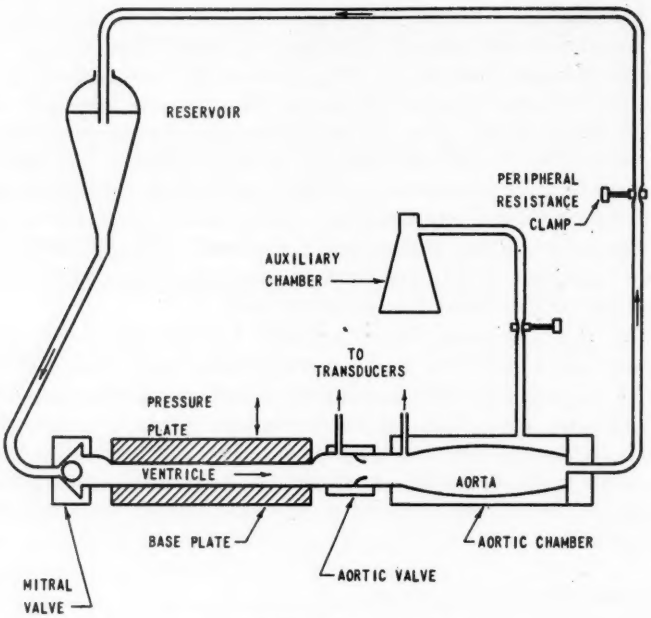


Fig. 1.—Cardiovascular simulator.

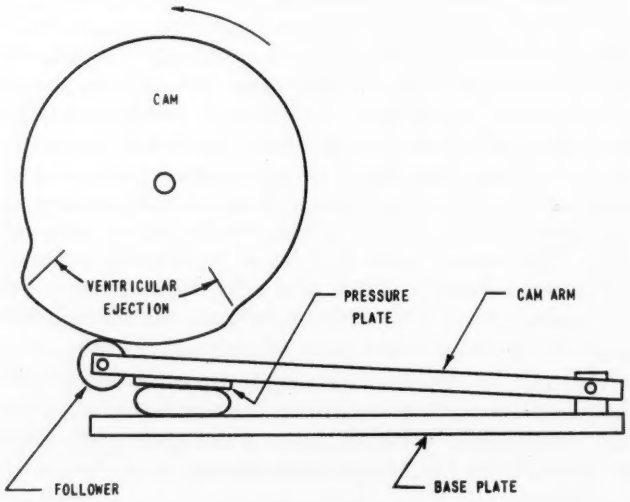


Fig. 2.—Ventricle analogue.

within the physiologic range. It can be shown by the principles of stress analysis that a straight-line relationship does not exist between volume and pressure for a thin-walled cylinder of perfectly elastic* material. The actual aortic pressure-volume curve, therefore, although simple in appearance, is a manifestation of the complex nature of the vessel walls.

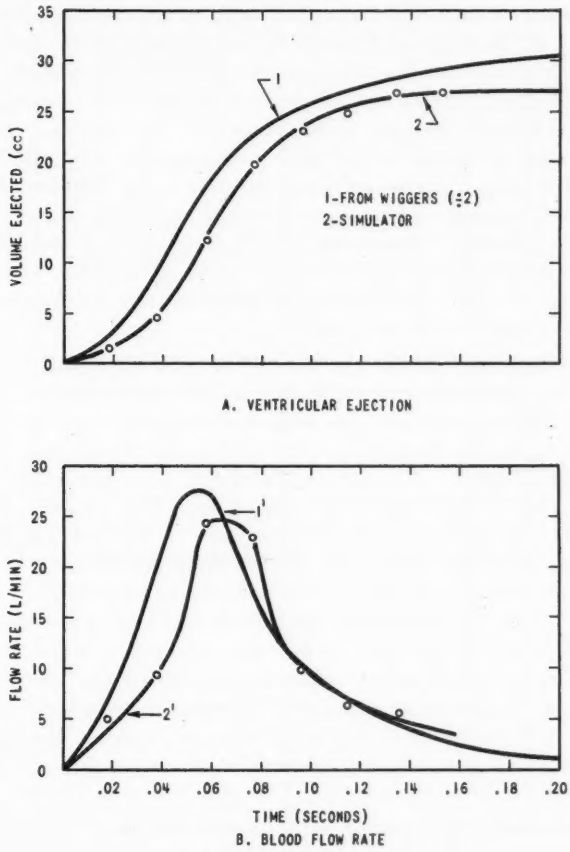


Fig. 3.—Ejection phase.

Another factor which greatly complicates the accurate simulation of blood flow is the relatively slow propagation of the arterial pulse along the aorta. If the aorta were acting as a simple container, there would be an equal increase in diameter along the entire vessel, and no traveling pulse would exist. It is known, however, that the root of the aorta distends to accommodate a relatively large volume of blood during ventricular ejection, and that the area of

*As used here, elasticity is an explicit term which refers to the direct proportion of stress (tension force) to strain (deformation of a material under stress).

distention travels down the aorta at a rate of 4 to 5 meters per second. Since this involves complex transient phenomena, empirical techniques were employed to obtain normal aortic behavior.

The aortic analogue consisted of gum rubber tubing (2.4 cm. diameter by 1.5 mm. wall) enclosed in an air chamber (7 cm. diameter by 26 cm. long). The volume of the air chamber was varied by partially filling it with water, and fittings were provided to allow adjustment of the gas pressure. A 500 ml. auxiliary air bottle was connected to the aortic chamber through a rubber tube to which a screw clamp was applied to restrict the passage of air. Experimentation showed that a simple air chamber could not be used for obtaining normal aortic pressure curves. When the size of the chamber was made large enough to result in proper aortic pulse pressures, the separation between the systolic and diastolic phases was lost, and the curve acquired a "saw-tooth" shape. Reducing the air volume so as to obtain a normally shaped curve resulted in high pulse pressures. It was empirically found that by reducing the aortic chamber air volume, connecting this chamber to an auxiliary chamber through an air restriction, and reducing the pressure of the air system, that nearly normal aortic curves could be produced.

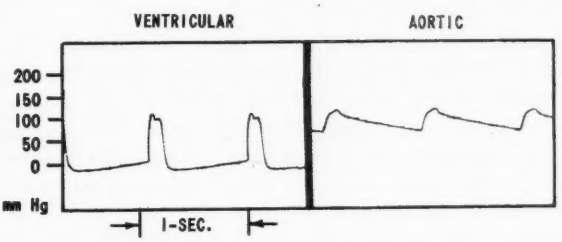
C. *Peripheral Resistance and Blood Viscosity.*—Peripheral resistance was applied to the system by a screw clamp on the rubber tube leading from the aorta to the liquid reservoir. The reservoir was placed approximately 40 cm. above the ventricle so as to provide sufficient diastolic fill pressure.

Viscosity is usually regarded as a property of a particular liquid, which changes only with composition and temperature. The viscosity of blood, however, depends also on flow conditions. Lamport[5] concluded that blood acts as a combined viscous-plastic fluid, and the in vitro performance of whole blood is such that its effective viscosity is a function of flow velocity and vessel diameter, the effect of these parameters on viscosity being more pronounced at higher hematocrit. Blood of less than 55 per cent hematocrit which flows in tubes, 3 mm. or greater in diameter, exhibits nearly pure viscous properties. From the standpoint of ventricular and aortic dynamics, therefore, the laws of viscous fluids apply. A 42 per cent glycerol solution was used as the blood analogue. At 20° C. such a solution has a viscosity of 4.1 centipoise, and at 25° C. the viscosity is 3.5.

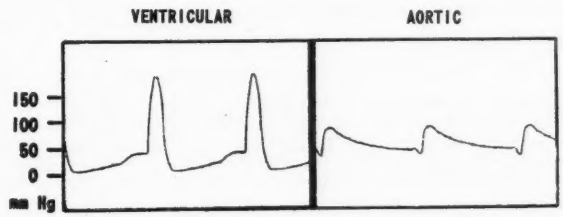
D. *Instrumentation.*—Large bore tubes were used to communicate ventricular and aortic pressures to Statham P23A strain gauge transducers. The ventricular recording system, which received the highest frequency components, was adjusted for slight underdamping to assure maximum frequency pass band without introducing significant artifact. Step input pressure tests indicated that at this condition the response was 3 db down at 12 c.p.s., and the resonant frequency was 45 c.p.s. The recording system, which was thus capable of reproducing more than the tenth harmonic of the fundamental, was adequate for physiologic pulses.[3, 8]

The output of each transducer circuit was fed to a cathode follower power amplifier from which three types of presentation were available: oscilloscope,

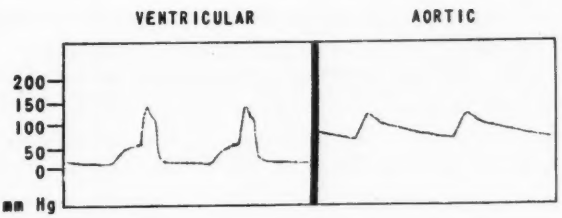
recorder, and oscilloscope switch. The last facilitated a twin beam effect so that the ventricular and aortic pressures could be simultaneously displayed on the same scale. The oscilloscope (Hewlett-Packard Model 130A) was used for calibration and for adjusting the simulator variables. Permanent charts were made with a two channel Brush Electronic Oscillograph (Model BL-202 recorder with Model BL-932 DC amplifier).



A. BALL CHECK VALVE



B. TEST VALVE (LEAFLET)



C. HUFNAGEL VALVE

Fig. 4.—Pressure curves.

III. METHOD OF VALVE EVALUATION

In order to establish reference curves and set the mechanical adjustments, the cardiovascular simulator was first operated with a ball check aortic valve. After the glycerol circuit was purged of air, 530 ml. of water were placed in the

aortic air chamber. Previous tests indicated that this reduction in chamber volume was necessary to achieve normal aortic distensibility. The air pressure in the chamber was then reduced to 130 mm. Hg below atmospheric pressure, a value which was also determined empirically. The simulator motor was started, and the peripheral resistance clamp adjusted until the desired diastolic pressure was obtained as indicated by the aortic pressure wave displayed on the oscilloscope. The clamp on the tube between the aortic chamber and the auxiliary bottle was then adjusted for the desired systolic pressure.

The above procedure established a "normal" cardiovascular system, and recorder charts were taken of the ventricular and aortic pressure curves (Fig. 4, *A*). The ball check valve was then removed and a test prosthetic aortic valve put in its place, care being taken that none of the simulator adjustments were moved. Pressure waves were recorded with the test valve in the otherwise "normal" cardiovascular system. Fig. 4, *B* shows the tracings from a cast leaflet type synthetic elastomer valve,* a high degree of stenosis being obvious. A Hufnagel valve[4] showed only slight stenosis (Fig. 4, *C*). As a confirmation of test reliability, the ball valve was reassembled in the simulator and pressures recorded. These charts were compared to the initial tracings to determine whether the simulator adjustments remained unchanged during the test.

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Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Fortieth Annual Meeting of The American Association for Thoracic Surgery will be held May 11, 12, and 13, 1960, in Miami Beach, Florida. Headquarters will be the Deauville Hotel.

Requests for Hotel Reservations

These should be mailed directly to Mrs. Mildred Sander, Reservation Manager, Deauville Hotel, Miami Beach, Florida. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere please communicate directly with the hotel of your choice.

Material for the Program

SCIENTIFIC PAPERS.—Abstracts of all papers proposed for presentation at the 1960 meeting *must be received on or before* **November 15, 1959,** otherwise they will not be considered by the Program Committee. These should be labeled "For Thoracic Surgery Forum" or "For Regular Program" depending upon the nature of the subject matter, in the same manner as in previous years. They should contain from 200 to 250 words that accurately reflect the content of the completed paper.

Six, repeat, six clearly legible copies of *each* abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, 308 Carondelet Building, 7730 Carondelet Avenue, St. Louis 5, Missouri.

Essayists selected for the program are reminded that papers presented at the meeting *must* be handed to the secretary *immediately* after their presentation. If they are not ready at that time there is a chance that they will not be published in THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee *not later than* **November 15, 1959,** otherwise the application will be deferred for consideration until the 1961 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signature on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Frank Gerbode, M.D.
Chairman of the Membership Committee
Stanford University Hospital
San Francisco 15, California

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Chairman of the Membership Committee should their applicants be held over for reconsideration a *second year.*